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The importance of low blood urea nitrogen levels in pregnant patients undergoing hemodialysis to optimize birth weight and gestational age

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Most published reports indicate that intensified hemodialysis results in better pregnancy outcomes. Here we studied clinical characteristics and the outcomes of 28 pregnant women receiving hemodialysis. We found an association between maternal blood data and birth weight, and gestational age and outcomes. There were 18 surviving infants who were followed up for one year. In the others there were 4 spontaneous abortions, 1 stillbirth, 3 neonatal deaths and 2 deaths after birth. Analysis of blood chemistry for 20 pregnancies from 12 weeks of gestation until delivery showed that the average hemoglobin level was significantly higher in the group that successfully delivered than in the unsuccessful group. There were significant negative relationships between the blood urea nitrogen (BUN) level and the birth weight or gestational age in the latter cohort. A birth weight equal to or greater than 1500 g or a gestational age equal to or exceeding 32 weeks corresponded to BUN levels of 48–49 mg/dl or less. Whether the low BUN is the direct cause of the improved outcome remains to be examined.

Kidney International (2009) **75,** 1217–1222; doi:10.1038/ki.2009.48; published online 25 February 2009

KEYWORDS: birth weight; BUN level; gestational age; hemodialysis; pregnancy

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Received 8 June 2008; revised 25 December 2008; accepted 7 January 2009; published online 25 February 2009

The pregnancy and successful delivery in a patient receiving maintenance hemodialysis (HD) was first reported in 1971.[1] In Japan, the first successful delivery was performed in 1977.[2] Since then, the number and incidence of pregnant patients receiving dialysis have been increasing, with the outcome being a marked improvement in infant survival. In 1999, Toma *et al.*[3] reported a 48.6% (36 out of 74) success rate in Japan. Ching-Yu Chou *et al.*[4] reported a success rate of 70.9% (83 out of 117) for patients treated between 1990 and 2006. These rates may indeed represent an overestimation, as large numbers of women may have had spontaneous miscarriages during earlier stages of their pregnancies. As the number of renal transplantation donors is insufficient in Japan, the duration of HD therapy is much longer than it is in other countries.[5] We have treated 33 pregnant women receiving HD from 1986 to 2007, which is the larger number ever reported at a single center; here, we have investigated the characteristics of these pregnancies.

RESULTS

Outcomes of pregnancies

The outcomes of the pregnancies are shown in Table 1. Of all 28 cases studied, 18 (64.3%) resulted in surviving infants who were followed up for a year.

Twenty-two pregnancies were preterm and only two pregnancies were full term. The most frequent reason for delivery was advanced labor (11 out of 22, 50.0%). The number of cesarean section deliveries was nine (9 out of 24, 37.5%). The most frequent reason for performing a cesarean was also a non-reassuring fetal status (6 out of 9, 66.7%).

We examined 11 pregnancies from 1986 to 1996 and 17 pregnancies from 1997 to 2007, and we compared the outcome of pregnancies between two groups. The rates of successful pregnancy were 63.6 versus 64.7%, respectively. The birth weights of newborns were not significantly different (1545.7 ± 730.2 versus 1311.0 ± 792.5 g, respectively; $P = 0.457$). The gestational ages at the time of delivery were also not significantly different (31.4 ± 4.7 versus 26.4 ± 10.6 weeks, respectively; $P = 0.154$).

Table 1 | Outcomes of the pregnancies

Subjects	Number	Percent
Number of pregnancies	28	
Death or survival		
Spontaneous abortion	4/28	14.3
Stillbirth	1/28	3.6
Neonatal death	3/28	10.7
Infant death	2/28	7.1
Surviving infants followed up for a year	18/28	64.3
Timing of delivery		
Preterm	22/24	91.7
Full term	2/24	8.3
Reasons for preterm delivery		
Spontaneous preterm delivery		
Advanced labor	11/22	50.0
Chorioamnionitis	2/22	9.1
Indicated preterm delivery		
Non-reassuring fetal status	5/22	22.7
Intractable hypertension	3/22	13.6
Worsening of maternal condition	1/22	4.5
Mode of delivery		
Vaginal	15/24	62.5
Cesarean section	9/24	37.5
Reasons for cesarean section		
Non-reassuring fetal status	6/9	66.7
Poor progress	1/9	11.1
Maternal indication	2/9	22.2

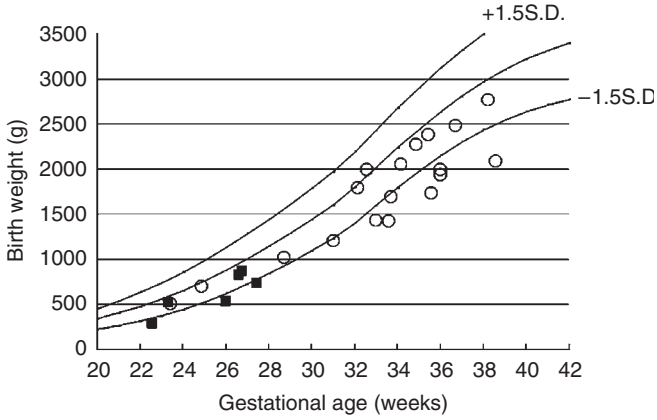

Figure 1 | Birth weights. ○: successful pregnancy, ■: unsuccessful pregnancy. The curves for the normal birth weight standard deviation (s.d.) were obtained from Norio S *et al.*[6]

Of the 28 pregnancies, except for the four cases that resulted in spontaneous abortions, the fetal growth curve of the remaining 24 cases is shown in Figure 1. In our hospital, most successful pregnancies were those that delivered infants whose birth weight was >1500 g.

Maternal and neonatal complications

The maternal and neonatal complications are shown in Table 2. Of the 11 patients who exhibited hypertension at some time during their pregnancy, eight patients required medications. Of the 21 infants, 9 were born with complications. The mean birth weight of these infants was 932.9 ± 454.5 g. Of the 9 infants with complications, 8 had a birth weight of <1500 g. Of the twenty-four newborns, 10 were light-for-date.

Table 2 | Maternal and neonatal complications

Subjects	Number	Percent
Maternal complications		
Polyhydramnios	11/28	39.3
Hypertension	11/28	39.3
Incompetent cervix	4/28	14.3
Hypotension	1/28	3.6
Neonatal complications[a]		
Retinopathy of prematurity	5/21	23.8
Respiratory distress syndrome	4/21	19.0
Patent ductus arteriosus	3/21	14.3
Chronic lung disease	3/21	14.3
Anemia	2/21	9.5
Hypotension	1/21	4.8
Sepsis	1/21	4.8
Intraventricular hemorrhage	1/21	4.8
Periventricular leukomalacia	1/21	4.8
Encephalopathy	1/21	4.8

[a]A total of 23 neonates survived at birth. Data were available for 21 of them.

Maternal characteristics and birth weight

The maternal characteristics are shown in Table 3. No statistical difference in the mean maternal age at delivery was seen between the successful group (34.4 ± 4.0 years) and the unsuccessful group (32.3 ± 4.8 years). No statistical difference in the period of dialysis treatment was seen between the successful group (3.6 ± 4.1 years) and the unsuccessful group (5.4 ± 5.0 years). We examined the mean dialysis time during pregnancy of 23 patients who had received regular HD before conception, except of the patients who started HD after conception or those who received HD only during their pregnancy. Their mean dialysis time (h per week) was 12.7 ± 2.5 in first trimester ($n=23$, median 12.0), it was 15.9 ± 3.1 in second trimester ($n=20$, median 15.4), and it was 18.4 ± 2.6 in third trimester ($n=13$, median 20.0). The mean maximum HD time ($n=23$) during pregnancy was 18.2 ± 3.9 h per week. No statistical difference in the mean maximum HD time was seen between the successful group (19.2 ± 3.3 h per week) and the unsuccessful group (16.3 ± 4.3 h per week). We could estimate the weekly dialysis Kt/V values in 13 successful cases and 4 unsuccessful cases. The value tended to be higher in the successful cases (2.98 ± 0.72) than in the unsuccessful cases (2.47 ± 1.04). The mean gestational age at the time of delivery was 28.3 ± 9.0 weeks. No statistical differences in the causes of end-stage renal disease were seen between the two groups. All the patients used human erythropoietin (rHuEPO) or received blood transfusions. No statistical differences in the use of rHuEPO, iron, or blood transfusion were seen between the two groups.

Table 3 | Maternal characteristics and birth weights

Variables	Total	Successful Group	Unsuccessful Group	*P*-value
Number	28	18	10	
Maternal age (years)	33.6 ± 4.3	34.4 ± 4.0	32.3 ± 4.8	NS
Duration of HD (years)	4.2 ± 4.5	3.6 ± 4.1	5.4 ± 5.0	NS
Maximum HD time (h per week)[a](median)	18.2 ± 3.9 (20.0)	19.2 ± 3.3 (20.0)	16.3 ± 4.3 (16.0)	NS
Birth weight (g)[b]	1414.0 ± 759.2	1747.4 ± 607.0	559.6 ± 277.0	<0.001
Cause of end-stage kidney disease				
Chronic glomerulonephritis	15 (53.6)	8 (44.4)	7 (70.0)	NS
Type I diabetic nephropathy	3 (10.7)	1 (5.6)	2 (20.0)	NS
Reflux nephropathy	3 (10.7)	3 (1.7)	0 (0.0)	NS
Henoch–Schonlein purpura nephritis	2 (7.1)	2 (11.1)	0 (0.0)	NS
Type II diabetic nephropathy	1 (3.6)	1 (5.6)	0 (0.0)	NS
Lupus nephritis	1 (3.6)	1 (5.6)	0 (0.0)	NS
Nephrotic syndrome	1 (3.6)	1 (5.6)	0 (0.0)	NS
Medullary sponge kidney	1 (3.6)	1 (5.6)	0 (0.0)	NS
Gestosis	1 (3.6)	0 (0.0)	1 (10.0)	NS
Anemia management				
Blood transfusion *N*(%)	9 (32.1)	5 (27.8)	4 (40.0)	NS
Human erythropoietin *N*(%)	24 (85.7)	15 (83.3)	9 (90.0)	NS
Iron *N*(%)	6 (21.4)	5 (27.8)	1 (10.0)	NS
Biochemical Parameters[c]				
Hemoglobin (g/100 ml)	9.3 ± 1.3	9.6 ± 0.9	8.3 ± 1.9	0.036
Albumin (g/100 ml)	3.4 ± 0.3	3.4 ± 0.3	3.4 ± 0.3	NS
Blood urea nitrogen (mg/100 ml)	50.7 ± 12.9	45.3 ± 8.3	66.9 ± 10.9	<0.001
Creatinine (mg/100 ml)	7.3 ± 1.9	6.7 ± 1.6	9.0 ± 1.4	0.010
Potassium (mEq/l)	4.1 ± 0.4	4.1 ± 0.3	4.4 ± 0.5	NS
Calcium (mg/100 ml)	9.0 ± 0.6	9.0 ± 0.4	8.9 ± 0.8	NS
Phosphate (mg/100 ml)	4.4 ± 0.8	4.2 ± 0.6	4.7 ± 1.2	NS

HD, hemodialysis; NS, not significant ($P > 0.05$).
[a]Of the 23 patients who had received regular HD before conception, 15 were successful cases and 8 were unsuccessful cases.
[b]The total number of infants was 25, because 3 cases underwent dilatation and curettage; 18 were successful cases and 7 were unsuccessful cases.
[c]We obtained biochemical data from 20 patients; 15 were successful cases and 5 were unsuccessful cases.

Biochemical parameters

The average of hemoglobin (Hb) level was significantly higher in the successful group than in the unsuccessful group (9.6 ± 0.9 versus 8.3 ± 1.9 g/100 ml, respectively; $P = 0.036$). The average of blood urea nitrogen (BUN) level was significantly lower in the successful group than in the unsuccessful group (45.3 ± 8.3 versus 66.9 ± 10.9 mg/100 ml, respectively; $P < 0.001$). The creatinine level was also significantly lower in the successful group than in the unsuccessful group (6.7 ± 1.6 versus 9.0 ± 1.4 mg/100 ml, respectively; $P = 0.010$). No significant differences in the averages of albumin, potassium, calcium, or phosphate levels were found between the two groups. The average of albumin level decreased from 3.6 ± 0.5 g/100 ml at about 12 weeks of gestational age to 2.9 ± 0.3 g/100 ml at the time of delivery.

Dry weight

The mean increased dry weight during the second trimester was 127.1 ± 167.4 g per week. The mean increased dry weight was 146.2 ± 183.0 g per week in the successful group ($n = 14$) and 65.0 ± 94.3 g per week in the unsuccessful group ($n = 3$), during the second trimester. The mean increased dry weight was 193.6 ± 111.0 g per week during the third trimester, but it was only in the successful group ($n = 11$).

Table 4 | Linear regression analysis of relationships of maternal characteristics with birth weight and gestational age

	Birth weight		Gestational age	
Variables	*r*	*P*-value	*r*	*P*-value
Maternal age (years)	0.063	0.791	0.167	0.483
Duration of HD (years)	−0.126	0.598	0.013	0.958
Hemoglobin (g/100 ml)	0.164	0.490	0.101	0.672
Albumin (g/100 ml)	−0.085	0.738	−0.098	0.699
Blood urea nitrogen (mg/100 ml)	−0.533	0.016	−0.504	0.023
Creatinine (mg/100 ml)	−0.429	0.059	−0.422	0.064
Potassium (mEq/l)	−0.008	0.977	0.098	0.707
Calcium (mg/100 ml)	0.050	0.849	−0.098	0.889
Phosphate (mg/100 ml)	−0.266	0.301	−0.292	0.255

HD, hemodialysis; *r*, correlation coefficient.

Association between maternal clinical and biochemical parameters, and birth weight

Table 4 shows the association between the birth weight, and the maternal clinical and biochemical parameters. We observed a negative relation between the birth weight and the BUN level ($r = -0.533$, $P = 0.016$). A birth weight of 1500 g corresponded to a BUN level of 49.0 mg/100 ml (Figure 2). The maternal serum creatinine level also tended to

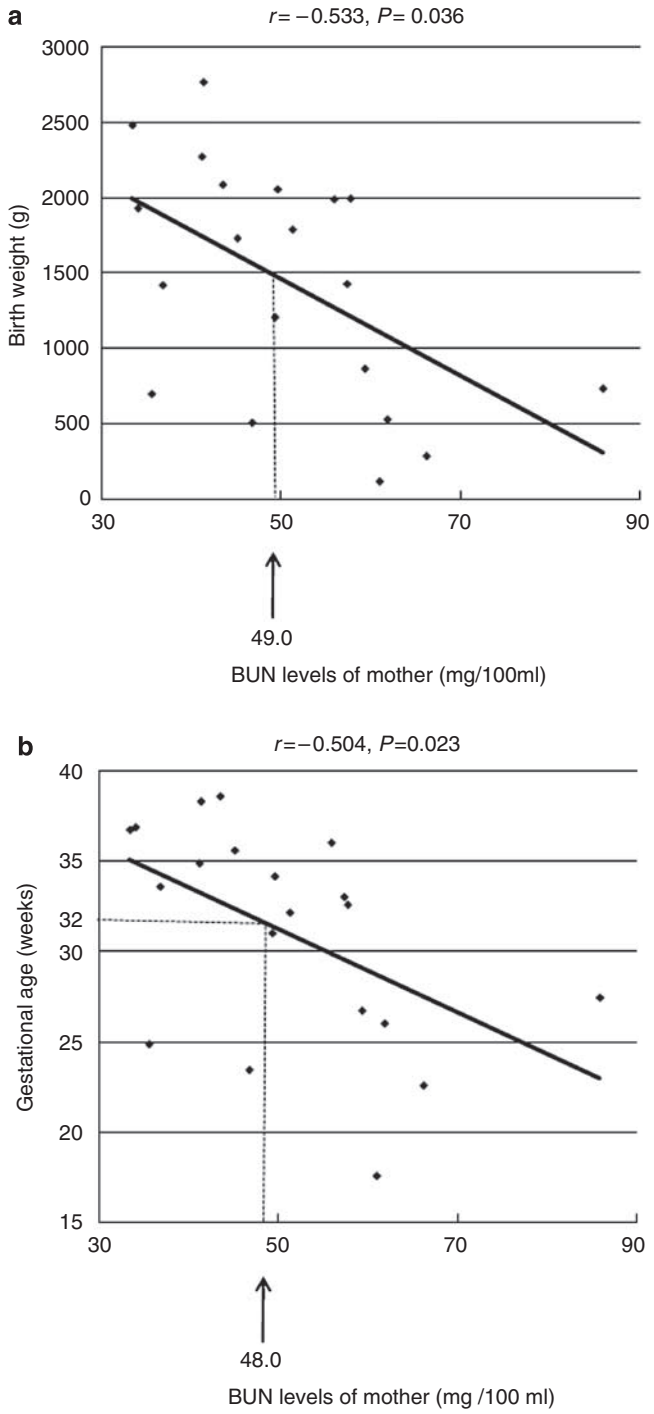

Figure 2 | Linear regression analysis of relationships of maternal blood urea nitrogen level with birth weight and gestational age. (**a**) Association between birth weight and maternal blood urea nitrogen (BUN) level. A birth weight of 1500 g corresponded to a BUN level of 49.0 mg/100 ml. (**b**) Association between gestational age and maternal BUN level. A gestational age of 32 weeks corresponded to a maternal BUN level of 48.0 mg/100 ml.

be negatively correlated with the birth weight. The maternal age, the duration of HD, and the Hb, albumin, potassium, calcium, and phosphate levels were not correlated with the birth weight.

Association between maternal clinical and biochemical parameters, and gestational age

Table 4 also shows an association between the gestational age, and maternal clinical and biochemical parameters. A negative correlation between the gestational age and the BUN levels was observed ($r = -0.504$, $P = 0.023$). The serum creatinine levels tended to be negatively correlated with the gestational age ($r = -0.422$, $P = 0.064$). A gestational age of 32 weeks corresponded to a BUN level of 48.0 mg/100 ml (Figure 2). The maternal age, the duration of HD, and the Hb, albumin, potassium, calcium, and phosphate levels were not correlated with the gestational age.

DISCUSSION

Premature delivery is the most important problem for pregnant women on dialysis, and a high rate of neonatal death exists. A non-reassuring fetal status was the most frequent cause of delivery and was also a major cause of cesarean section. One hundred fifty pregnant women with chronic kidney disease, none of whom had received dialysis, were studied in 1963, and the most important factor influencing fetal mortality was reported to be the maternal BUN level.[7] A favorable fetal outcome might be due to a less azotemic environment. An increase in the dose of HD treatment can reduce the azotemic status of the maternal serum. Prolonged or intensive dialysis during pregnancy results in longer gestational periods, higher fetal birth weights, and greater fetal survival.[8–12] In our hospital, most successful pregnancies were those that delivered infants whose birth weight was >1500 g. We found that the BUN level was negatively correlated with the birth weight and a birth weight of 1500 g corresponded to a BUN of 49.0 mg/100 ml. It is known that 32 weeks of gestation is a meaningful time for decision making on interventions. Robertson *et al.*[13] analyzed neonatal outcomes and concluded that the threshold, defined as the gestational week at which the incidence of complications attributable to preterm delivery became indistinguishable from those of term infants, was between 32 and 34 weeks. We also revealed that the BUN level was negatively correlated with the gestational age, and a gestational age of 32 weeks corresponded to a BUN level of 48.0 mg/100 ml. Therefore, we suggest keeping the maternal BUN level below 48 mg/100 ml. No randomized prospective trials of pregnant women on dialysis exist, but retrospective data have suggested that keeping a maternal pre-dialysis BUN level below 50 mg/100 ml may be an appropriate goal.[9,14] This target was almost the same as our suggestion. For pregnant patients with chronic kidney disease who had not received HD and whose BUN level was maintained above 50 mg per 100 ml, we think that it is better that dialysis treatment is started to reduce the azotemic environment. Recently, Barua *et al.*[12] reported the outcomes of seven pregnant women on nocturnal HD. The mean nocturnal HD treatment time increased to 48 ± 5 h per week and normal physiological pre-dialysis BUN concentrations could be maintained throughout the pregnancies. The mean gestational age was 36.2 ± 3.0

weeks, the mean birth weight was 2417.5 ± 657.0 g, and there were few maternal and fetal complications. These noteworthy good outcomes may due to the intensive HD treatment, which allowed the serum BUN levels to be kept within normal range.

Delayed confirmation of pregnancy is common among women receiving HD because these patients are often unaware of their pregnancy, as they usually have irregular or anovulatory menstrual cycles.[15,16] In some of our patients, conception was confirmed too late, as their BUN level was kept high until the second trimester and their infants had some complications. If a woman receiving HD wishes to get pregnant, she and her attending physician should discuss the issue before conception, and the dialysis dose should be planned accordingly.

Iron and rHuEPO requirements have been reported to increase in the pregnant patients receiving HD.[12,14] Although anemia is a typical feature of pregnancy, pregnant patients may be resistant to rHuEPO because of cytokine production during gestation.[9] All the patients in our study underwent blood transfusions or used rHuEPO. The Hb level was significantly higher in the successful group than in the unsuccessful group ($P = 0.036$). Holley *et al.*[14] recommended maintenance of the Hb level at 10–11 g/100 ml for a better outcome of pregnancy in HD patients. Thus, the maternal Hb level may affect fetal, neonatal, and infant survivability. Further investigation is necessary to determine the optimal Hb level.

The mean time between the start of HD and conception was 4.2 ± 4.5 years. Patients receiving long-term HD have generally been reported to have difficulties having successful deliveries.[17] In our study, however, the duration of HD was not statistically different between the successful group and the unsuccessful group. One of our patients was 42 years old at delivery, had received regular HD treatments for 18 years, and had a successful pregnancy.

Haase *et al.*[18] reported that in five pregnant women receiving frequent and intense dialysis treatments (at least 24 h per week), who had high protein intakes (approximately 1.5 g/kg per day), and whose average weight gain was 282 ± 193 g per week, the serum albumin levels improved and their BUN levels were controlled. Another report has recommended a protein intake of 1.2 g/kg per day.[14] In our patients, the mean serum albumin level decreased from 3.6 ± 0.5 g per 100 ml at 12 weeks of gestational age to 2.9 ± 0.3 g/100 ml at the time of delivery. Of the 23 alive neonates, 10 (43.5%) were light-for-date at birth. In general, the gain in maternal body weight among pregnant Japanese women is about 250 g per week in the third trimester; however, the mean weight gain of our patients was 193.6 ± 111.0 g per week. A higher food intake and a larger HD dose compared with our patients might be better for fetal growth. Further consideration of the appropriate protein or caloric intake of pregnant women receiving dialysis is needed.

Polyhydramnios is one of the most important complications affecting infant mortality, and this condition is common in this population, although its cause is unclear. In our study, an inappropriate maternal dry weight setting seemed to be one of the causes of polyhydramnios. The increase in the maternal circulating plasma volume may cause the fetal plasma volume and the amount of fetal urine to increase, resulting in polyhydramnios. In pregnant dialysis patients, estimating the dry weight is even more difficult because of pregnancy-induced weight gains and the need to avoid maternal hypotension during treatments. We evaluated the fetal growth and the amniotic fluid volume using sonographic examinations, the maternal atrial natriuretic peptide level, and the maternal blood pressure to assess the volume status and ultrafiltration needs of the pregnant patients undergoing HD treatment. After the first trimester, weight gain has often been reported to be linear, with a gain of approximately 500 g per week.[19] But in our study, the weight gain was 146.2 ± 183.0 g per week during the second trimester and 193.6 ± 111.0 g per week during the third trimester in the successful group. This difference may be partly due to racial differences and/or a shortage of food intake, as described above.

In our observation, success was achieved in three out of four (75.0%) patients in whom HD was started after conception, and in 15 out of 24 (62.5%) patients in whom HD was started before conception. Thus, the success rate tended to be higher in the patients in whom HD was started after conception. Women in whom dialysis is initiated during pregnancy may, in general, have a better prognosis than in women treated with HD at the time of conception. Therefore, we excluded the four patients in whom the HD was started after conception, and found that there was a negative correlation between the BUN and the birth weight ($P = 0.044$, $r = -0.508$), and that the Hb level tended to be higher in the successful group (9.75 ± 0.88 g/100 ml) than in the unsuccessful group (8.38 ± 2.12, $P = 0.080$).

There were several limitations of our study. Firstly, it was a retrospective case series and it was a single-center study. Secondly, there were a few missing data, the total number of blood examinations was 204 points in 20 patients in this study, and the number of lacks of both BUN and creatinine were 13 (0.06%) points, and the number of lacks of Hb was 15 (0.07%) points, respectively. Finally, most of data were available from gestation age of 12 weeks in our patients; however, it may be necessary to investigate from the period of organogenesis of the early first trimester.

We found that the maternal Hb level during pregnancy was associated with successful pregnancy. We also found that the maternal BUN level during pregnancy was associated with successful pregnancy, and it was negatively correlated with birth weight and gestational age. A birth weight of 1500 g corresponded to a BUN level of 49.0 mg/100 ml, and a gestational age of 32 weeks corresponded to a BUN level of 48.0 mg/100 ml. We think that intensive dialysis is effective for successful pregnancy because the low BUN level associates with birth weight and gestational age.

MATERIALS AND METHODS

Patients and dialysis

We sequentially examined 33 pregnancies in 31 women receiving HD at the Tokyo Women's Medical University Hospital from 1986 to 2007. Four pregnant women decided to terminate their pregnancies because of social factors, and elective abortions were performed. One woman had an extrauterine pregnancy. The remaining 28 cases decided to continue their pregnancies and were enrolled in this study. Twenty-three patients had received regular HD before conception, two patients started HD after conception, two patients with chronic kidney disease received HD only during their pregnancy to reduce the azotemic environment, and one patient undergoing continuous ambulatory peritoneal dialysis had combination HD treatment during her pregnancy. Four pregnancies resulted in spontaneous abortions, one resulted in a stillbirth, three resulted in neonatal death, two resulted in infant death, and 18 resulted in surviving infants who were followed up for 1 year. Neonatal complications were investigated in 21 of them, for whom the data were available. We examined the relationships between the maternal clinical and biochemical parameters, and birth weight or gestational age. Gestational age was determined based on last menstrual period and standard obstetric ultrasonography. This study was conducted in accordance with the recommendations of the Declaration of Helsinki, and informed consent was obtained from all participating patients. It was a retrospective case series.

Patients were delivered with the onset of active labor, intrauterine infection, worsening of maternal condition and non-reassuring fetal status. Cesarean sections were carried out for those patients who had undergone cesarean section earlier, as well as those in whom non-reassuring fetal status or fetal malpresentation was present.

Biochemical parameters

The maternal blood examinations were performed at the start of dialysis. We could gain biochemical data of 20 patients. Biochemical parameters like BUN, creatinine, and Hb were investigated every 2 weeks during the period from 12 (except of two: one was from week 14 and one was from week 16) weeks of gestation age until delivery. The weighted average values might be more important for the outcome of pregnancy than one-point data. Therefore, the weighted average values were used in this study. The weekly dialysis Kt/V was calculated as reported earlier.[20]

Dry weight

We obtained information on dry weight throughout the pregnancies of our patients, starting at 22–27 weeks of gestation in 17 patients and at 28 weeks in 11 patients, and continuing until delivery. We analyzed increased dry weight at several time points during the second and third trimesters.

Definitions

Hypertension was defined as a systolic blood pressure of 140 mm Hg or more, or a diastolic blood pressure of 90 mm Hg or more, and/or the current use of antihypertensive drugs. Neonatal death was defined as death <28 days after birth. Infant death was defined as death from 28 days to 1 year after birth. We defined a successful pregnancy as one in which the delivery was without maternal mortality and the infant survived >1 year. Polyhydramnios was defined as an amniotic fluid index of >25 cm or the presence of a large amniotic fluid pocket of >8 cm, as measured using ultrasonography.

Statistical analysis

Data were reported as the means (s.d.) The Student t-test was used to compare continuous variables between the two groups. The χ^2 or Fisher exact probability test was applied for categorical data. A simple linear regression analysis was used to examine the relationships between two continuous variables. A probability <0.05 was considered significant. All statistical calculations were performed with JMP 5.1 software (SAS for Windows, Cart, NC, USA).

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

We thank Dr Nakanishi for data collection. We also thank Dr Shimizu for statistical advice.

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