Successful Pregnancies on Nocturnal Home Hemodialysis

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Background and objectives: Women of childbearing age on conventional hemodialysis (CHD) have decreased fertility when compared with the general population. Even in women who conceived, maternal morbidity and fetal mortality remained elevated. We hypothesized that nocturnal hemodialysis (NHD) (3 to 6 sessions per week, 6 to 8 h per treatment), by augmenting uremic clearance, leads to a more hospitable maternal environment and therefore superior outcomes in fertility and pregnancy compared with CHD.

Design, setting, participants, and measurements: This is a descriptive cohort study of all female patients achieving pregnancy and delivering a live infant while on NHD at the University Health Network, St. Michael's Hospital, and Humber River Regional Hospital from 2001 to 2006 in Toronto, Canada. Our primary objective was to describe maternal and fetal outcomes in addition to the changes in biochemical parameters after conception in our cohort.

Results: Our cohort included five patients (age range, 31 to 37 yr) who had seven pregnancies while on NHD and delivered six live infants. All had previously been on CHD, but none conceived during that time. In all patients, the amount of hemodialysis was increased (from a weekly mean of 36 ± 10 to 48 ± 5 h; $P < 0.01$) after pregnancy was diagnosed. Mean predialysis blood urea and mean arterial BP were maintained within normal physiological parameters. The mean gestational age of the cohort was 36.2 ± 3 wk and the mean birth weight was 2417.5 ± 657 g. The maternal and fetal complications observed in the cohort included intrauterine growth restriction or small for gestational age ($n = 2$), preterm delivery (<32 wk) ($n = 1$), and shortened cervix threatened labor ($n = 1$). Anemia was accentuated during pregnancy, and intravenous iron and erythropoietin requirements were increased. To maintain normal physiological indices for plasma phosphate, an augmented dialysate phosphate supplementation regimen was required.

Conclusions: NHD may allow for improved fertility. Delivering a live infant at a mature gestational age is feasible for patients on NHD. Our cohort tended to have fewer maternal and fetal complications compared with historical controls. Hemoglobin and phosphate levels must be monitored with treatment adjusted accordingly.

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Women of childbearing age on conventional hemodialysis (CHD) (4 h per treatment; 3 sessions per week) and peritoneal dialysis are known to have decreased fertility and poor infant survival compared with the general population (1). During the 1990s, the authors of the Registry of Pregnancy in Dialysis Patients reported a conception rate of 2.2% in >6000 American women of childbearing age who underwent chronic dialysis, with a corresponding infant survival rate of 42% (2). In the limited number of women that conceived while on CHD, the weekly duration of hemodialysis has traditionally been increased during pregnancy. Retrospective data has suggested that maintaining a predialysis blood urea nitrogen (BUN) value ≤50 mg/dl leads to a longer gestation and an increased likelihood of a successful pregnancy (3). Although the exact mechanism for decreased fertility and increased fetal mortality is unknown, the effect of uremia-related aberrations on the hypothalamic-pituitary-ovarian axis and maternal host environment may explain in part these poor outcomes (4).

Nocturnal hemodialysis (NHD), which provides 8 to 10 h of renal replacement therapy during sleep, 3 to 7 nights per week, delivers augmented uremic clearance (5). We postulate that minimization of the uremic milieu leads to restoration of a more hospitable maternal environment. We present the clinical outcomes and biochemical changes of five women who conceived and delivered six live infants while on NHD in Toronto, Canada, from 2001 to 2006.

Concise Methods

This is a retrospective study using prospectively collected data. The primary objective of the study was to describe maternal and fetal outcomes as well as changes in clinical and biochemical indices before and after conception. Institutional research ethics board approvals were obtained from all participating hospitals.

Study Population

Subjects included female patients who conceived and delivered live infants while on NHD at the University Health Network, St. Michael's Hospital, or Humber River Regional Hospital between 2001 and 2006.

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Table 1. Pregnancy outcomes[a]

	Number of Weeks at Delivery	Mode of Delivery	Baby's Birth Weight (g)	Baby's APGAR Scores at 1 and 5 min
Patient 1	36	C/S	2020	9/9
Patient 2: Pregnancy 1	38	SVD	3000	5/8
Patient 2: Pregnancy 2	37^{4}	SVD	2785	9/9
Patient 3	36^{5}	Induced labor, vacuum extraction	2690	6/9
Patient 4	38^{5}	C/S	2750	8/9
Patient 5	30	SVD	1260	5/7

[a]C/S, cesarean section; SVD, spontaneous vaginal delivery. Superscript numerals indicate days.

Clinical information, including maternal and fetal outcome data, were obtained by reviewing hospital and hemodialysis charts. Biochemical and hematological parameters (complete blood count, urea, creatinine, albumin, calcium and phosphate) were obtained from the hospital computer records at baseline and serially in monthly intervals through the duration of pregnancy. In all cases, antenatal care was conducted by an obstetrician specialized in high-risk pregnancy care working closely with a designated nephrologist.

Hemodialysis Prescription

NHD treatments before pregnancy consisted of hemodialysis at home for 7 to 8 h, 3 to 6 nights per week. After conception, NHD treatments were increased to 7 to 8 h, 5 to 7 nights per week. Blood flow and dialysate flow rates were 300 to 400 ml/min and 500 to 750 ml/min, respectively. F80 polysulfone dialyzers (Fresenius Medical Care, Lexington, MA) or Exceltra 120 dialyzers (Baxter, Chicago, IL) were used.

Dialysate composition was as follows: sodium, 137 to 140 mEq/L (mmol/L): potassium, 1.5 to 2 mEq/L (mmol/L); bicarbonate, 35 mEq/L; and calcium 6 to 7 mg/dl (1.5 to 1.75 mmol/L).

Statistical Analysis

Data are reported as a monthly mean with SD for all six pregnancies. A *t* test or Wilcoxon-rank test was used for comparison of continuous variables during gestation. Repeated-measure ANOVA was used to ascertain changes in a parameter over time. A two-tailed P value <0.05 (SPSS-14, SPSS Inc., Chicago, IL) was required for significance.

Results

Five female patients with ESRD were included in this cohort study. There were a total of seven pregnancies that resulted in six live births. One patient electively terminated her first conception because of the suggestion of a molar pregnancy. The pathological findings ultimately concluded that it had been a normal intrauterine gestation. All seven pregnancies occurred while the women were on NHD. There were 45 women of childbearing age (14 to 44 yr) on NHD in Toronto from 2001 to 2006, which translated to a conception rate of 15.6%.

The mean age at the time of conception was 32 ± 4 yr. The mean duration of NHD before pregnancy was 3 ± 2 yr. After conception, the number of hours prescribed per week of dialysis increased from 36 ± 10 to 48 ± 5 ($P < 0.01$). All five patients had previously been on CHD. One patient had previously been on peritoneal dialysis. Patients 4 and 5 received kidney transplants before converting to NHD. Patient 5 had two kidney transplants. Patient 3 had an orthotopic liver transplant. None had significant residual renal function.

The primary causes of renal failure included polycystic kidney disease ($n = 1$), IgA nephropathy ($n = 1$), calcineurin inhibitor toxicity ($n = 1$), hypoplastic kidney ($n = 1$), and unknown cause ($n = 1$).

Pregnancy outcomes are summarized in Table 1. Patient 1 had ultrasonographic evidence of intrauterine growth restriction and underwent a cesarean section at 36 wk, delivering a newborn that weighed 2020 g. Patient 2 had two spontaneous vaginal deliveries. The first pregnancy of patient 2 was previously reported in detail (6). The gestational ages were 37 wk, 4 days and 38 wk with birth weights of 3000 g and 2785 g, respectively. Patient 3 was induced at 36 weeks, 5 days because of multiple comorbid conditions including orthotopic liver transplantation and pancytopenia. She had a vaginal delivery that required vacuum extraction, which resulted in the birth of an infant weighing 2690 g. Patient 4 presented at 38 weeks, 5 days with a small amount of bloody vaginal discharge and was admitted for induction of labor. Because of failure to progress and nonreassuring fetal heart rate, she ultimately delivered by cesarean section a healthy newborn weighing 2750 g. Patient 5 had a spontaneous vaginal delivery at 30 wk. The newborn was small for gestational age (20th percentile) and weighed 1260 g. Taken together, the mean gestational age of the cohort was 36.2 ± 3 wk and the mean birth weight was 2417.5 ± 657 g. The maternal and fetal complications observed during the course of each pregnancy are summarized in Table 2.

The BP recordings during pregnancy are summarized in Table 3. During the entire period of gestation, the mean systolic and diastolic BP remained within normal physiological ranges. However, two required antihypertensive medications. Patient 2 was treated with 250 mg alpha methyldopa twice a day during the third trimester of both of her pregnancies. Patient 5 required 200 mg labetalol twice a day beginning in the second trimester. The mean monthly target weights are shown in Table 3.

The changes in metabolic indices throughout gestation are summarized in Table 4. As a result of the increase in dialysis prescription, the pre- and postdialysis BUN decreased progressively during gestation. Anemia was accentuated during pregnancy and intravenous iron and erythropoietin requirements were increased. Pre- and postdialysis serum calcium and phosphate levels fluctuated throughout gestation. To maintain normal physiological indices for plasma phosphate, an augmented dialysate phosphate supplementation regimen was required. Serum albumin decreased progressively throughout pregnancy.

Table 2. Maternal and fetal complications[a]

	Complications
Patient 1	IUGR
Patient 2: Pregnancy 1	Neonatal intensive care monitoring (1 d) Neonatal jaundice
Patient 2: Pregnancy 2	Cord entanglement
Patient 3	Shortened cervix at 25 wk
Patient 4	Vaginal spotting at 18, 22, and 38 wk, 5 days
Patient 5	Small for gestational age (20th percentile) Neonatal intensive care monitoring (7 d)

[a]IUGR, intrauterine growth restriction.

Discussion

Pregnancy for women of childbearing age on conventional renal replacement therapy occurs infrequently and has been associated with increased maternal and fetal complications (1). NHD is an emerging mode of intensive hemodialysis that has been shown to offer multiple clinical advantages compared with CHD (5). Our study is consistent with the concept that fertility is preserved in women on NHD. Furthermore, this study demonstrates that pregnancy and live birth is feasible while undergoing NHD. Our cohort tended to have fewer maternal and fetal complications as well as longer gestation periods compared with the published literature.

Fertility is decreased in patients with ESRD. For a large number of women, secondary amenorrhea occurs after the onset of chronic kidney disease and ESRD because of anovulation from disruption of the hypothalamic-pituitary-ovarian axis (4). The luteal hormone surge and estradiol peak that usually occurs mid- to late-menstruation has been shown to be absent in uremia. The mechanism by which this occurs remains unclear. One contributing factor may be the hyperprolactinemic state that is observed in women with ESRD (7). Interestingly, normalization of prolactin with bromocriptine, however, rarely leads to normal menstruation in ESRD patients and thus other factors must contribute. It is therefore interesting to note that augmented uremia management *via* NHD in our cohort was associated with a relatively higher conception rate of 15.6%. In addition, a search of the Toronto high-risk pregnancy database in an attempt to identify potential control patients revealed that there had only been two pregnancies in patients on CHD during the same era. It is therefore tempting to speculate that enhanced uremia control *via* NHD may restore the normal reproductive endocrine functions, which will require further prospective evaluations.

There is limited evidence to suggest that increasing hemodialysis hours improves pregnancy outcomes, specifically with respect to gestational age, birth weight, and infant survival (2,8). In a large registry study performed in the United States, there was a nonsignificant trend toward better survival and decreased prematurity in patients who received >20 h of dialysis per week (2). Similar results were reported by investigators who found a correlation between birth weight and hours of dialysis delivered during pregnancy (1). Several large surveys also confirmed that infants born to women on dialysis tended to be premature, with an average gestation of 32 wk (1,3,9,10). In contrast, the mean gestational age and birth weight in our NHD cohort was 36.2 ± 3 wk and 2417.5 ± 657 g, respectively. What potential advantages may NHD offer to improve pregnancy outcomes?

Common maternal complications observed in the ESRD population during pregnancy include hypertension and polyhydramnios (11). The pathogenesis of maternal hypertension in ESRD is complex, but hypervolemia and inappropriate elevated total peripheral resistance are likely central to the refractory nature of this comorbid condition. In addition, ESRD patients have an increased risk of developing preeclampsia. Common to both hypertension in ESRD and preeclampsia is the impairment in vascular responsiveness. Emerging data also focus on the potential pathogenetic role of placental insufficiency as a trigger and promoter of hypertension and preeclampsia in our patient population (12). NHD, by doubling the dialysis frequency and intensifying treatment duration, has been shown to decrease total peripheral resistance and

Table 3. Average blood pressure and weight each month of pregnancy

	Month								
	1	2	3	4	5	6	7	8	9
Systolic blood pressure (mmHg)	122 ± 24	119 ± 15	114 ± 10	118 ± 10	119 ± 11	112 ± 18	122 ± 16	117 ± 21	117 ± 24
Diastolic blood pressure (mmHg)	75 ± 20	76 ± 15	74 ± 10	81 ± 12	79 ± 12	73 ± 11	72 ± 9	80 ± 10	77 ± 11
Postdialysis weight (kg)	56.5 ± 4	57.5 ± 5	57.5 ± 5	58.7 ± 4	60.4 ± 5[a]	64.0 ± 6[a]	67.2 ± 7[a]	69.5 ± 7[a]	72.3 ± 9[a]

[a]$P < 0.05$ compared with baseline.

Table 4. Biochemical indices during pregnancy[a]

	Month								
	1	2	3	4	5	6	7	8	9
Hemoglobin (g/L)	117 ± 14	104 ± 20	109 ± 14	107 ± 8	110 ± 10	112 ± 16	110 ± 13	107 ± 18	114 ± 8
Erythropoietin (units/wk)	15,667 ± 12,291	18,000 ± 10,954[b]	21,800 ± 19,212[b]	26,000 ± 17,978[b]	29,000 ± 16,186[b]	28,667 ± 15,680[b]	29,333 ± 16,281	42,800 ± 43,441[b]	23,333 ± 7024[b]
IV iron (mg/wk)	50 ± 50	75 ± 79	65 ± 78	75 ± 79	75 ± 79	69 ± 78	66 ± 80	82 ± 81	100 ± 0
Dialysate sodium phosphate concentration (mmol/L)	0.53 ± 0.57	0.68 ± 0.43	0.58 ± 0.42	0.61 ± 0.47	0.75 ± 0.56	0.75 ± 0.78	1.1 ± 0.71[b]	1.0 ± 0.81[b]	0.57 ± 0.30
Predialysis phosphate concentration (mmol/L)	1.1 ± 0.4	0.8 ± 0.3	1.2 ± 0.7	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.4	0.9 ± 0.4	1.1 ± 0.4	1.3 ± 0.3
Postdialysis phosphate concentration (mmol/L)	0.8 ± 0.3	0.8 ± 0.4	1.2 ± 0.7	0.9 ± 0.5	0.7 ± 0.2	0.8 ± 0.4	0.8 ± 0.2	0.8 ± 0.1	0.9 ± 0.2
Predialysis calcium concentration (mmol/L)	2.5 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.2	2.4 ± 0.1	2.5 ± 0.1	2.4 ± 0.1	2.4 ± 0.2	2.5 ± 0.2
Postdialysis calcium concentration (mmol/L)	2.7 ± 0.1	2.6 ± 0.2	2.6 ± 0.1	2.5 ± 0.1	2.6 ± 0.1	2.6 ± 0.1	2.5 ± 0.1	2.6 ± 0.2	2.5 ± 0.1
Predialysis BUN (mmol/L)	14.0 ± 11	11.5 ± 8	12.0 ± 8	10.3 ± 9	7.6 ± 3[b]	10.0 ± 7[b]	8.5 ± 6[b]	8.0 ± 4[b]	8.0 ± 4[b]
Postdialysis BUN (mmol/L)	2.3 ± 2.4	3.2 ± 4.6	1.7 ± 1.4	1.6 ± 1.6	1.0 ± 0.4	1.0 ± 0.5	1.1 ± 1.3	1.3 ± 0.7	1.3 ± 0.7
Albumin (g/L)	38 ± 3	36 ± 3	35 ± 2	35 ± 3	33 ± 3	32 ± 3[b]	30 ± 3[b]	29 ± 2[b]	28 ± 2[b]

[a]IV, intravenous; BUN, blood urea nitrogen.
[b]$P < 0.05$ compared with baseline.

ameliorate the oscillatory nature of volume overload in ESRD (13,14). It is important to note that we were able to maintain the BP of our cohort within physiological ranges with minimal requirements for antihypertensive medications. In the future, systemic and placental hemodynamic monitoring might provide additional insights into the pathogenesis of maternal hypertension in patients with ESRD. Finally, it is hypothesized that increased placental urea leads to fetal solute diuresis and to polyhydramnios (11). Intensive hemodialysis has been purported to decrease the risk of preterm labor and postpartum infant complications by reducing predialysis BUN levels and thereby preventing polyhydramnios (6). In our cohort, we were able to maintain normal physiological predialysis urea concentration during their pregnancies. None of our patients had polyhydramnios, reiterating the importance of intensive nightly hemodialysis.

A number of other challenges exist in managing pregnant patients on renal replacement therapy. As reported in the literature, and also as demonstrated in this study, iron and erythropoietin requirements increased (3). Although anemia is a typical feature of pregnancy, it has been speculated that pregnant patients are resistant to erythropoietin because of cytokine production during gestation (1). Furthermore, our patients demonstrated the need for increased dialysate phosphate additive. This enhanced requirement may be a reflection of the increased metabolic demand from the fetus and/or augmented removal from nightly hemodialysis. Phosphate and acid/base abnormalities during pregnancy have the potential to impact on maternal and fetal bone architecture and deserve further investigation.

This study is limited by its observational nature and its small sample size. Furthermore, we were not able to compare our NHD cohort with a representative control group on CHD during the same era. The lack of control cases implies a low fertility rate among female patients of childbearing age on conventional renal replacement therapy. Finally, we are unable to refute the possibility that our observed pregnancy outcomes are derived from intensive fetal monitoring or improved compliance rather than from augmented hemodialysis dose delivery. It should be noted, however, that recent data showed that frequent fetal ultrasound monitoring had only a modest effect on pregnancy outcomes in our patient population (15).

NHD may lead to improved fertility, possibly by minimizing uremia-related hormonal and hemodynamic derangements. Our study also demonstrates the feasibility of delivering a mature live infant while on NHD. Although pregnancy and fetal complications still exist, these tended to be less severe than what has been described in the literature to date. Therefore, NHD may have a role in family planning for those female patients of childbearing age expressing an interest in conception.

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Disclosures

None.

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See related editorial, "Pregnancy in Women on Dialysis: Is Success a Matter of Time?" on pages 312–313.