The Placenta Effect: Risk Factors for Adverse Fetal Outcomes in Pregnant Dialysis Patients

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Pregnancy in women on dialysis is a rare, but complex, clinical situation that nephrologists increasingly face. Historically, maternal and fetal outcomes in the setting of dialysis have been poor, but more recent case series have suggested that women can have successful pregnancies on dialysis with more intensive therapy. In this issue of *Kidney International Reports*, Luders and colleagues present the largest case series of pregnant women on dialysis, with a description of 93 unique pregnancies in their tertiary center in Sao Paulo, Brazil. The authors reported a successful delivery rate of 89.2%, as well as risk factors positively and negatively associated with fetal outcomes. They also offered useful clinical information that can be applied to the care of young women on dialysis.

Several decades ago, the available literature suggested that fetal survival rates in women on dialysis were in the range of 20% to 50%. Risks to the fetus included prematurity, low birth weight, and neonatal death. Despite these discouraging early reports, there was a signal that the amount of both residual renal function and dialysis intensity was associated with improved outcomes. This was demonstrated clearly in a 2009 study by Asamiya et al., which showed that blood urea nitrogen (BUN) levels were negatively associated with low birth weights. In that study, pregnancies that were delivered at ≥32 weeks and had birth weights >1500 g had all achieved BUN levels of <48 to 49 mg/dl.

These findings were further supported by Luders et al. in their 2010 report of 53 pregnancies that demonstrated a 87% successful delivery rate with an intensive dialysis regimen of 2 to 3 hours of dialysis, 6 times per week (average 15 hours/week). The strongest predictor of adverse fetal outcomes, including perinatal death or extremely premature delivery before 30 weeks of gestation, was preeclampsia (57.1% of women with adverse fetal outcomes vs. 5.3% without adverse fetal outcomes; \( P < 0.001 \)). The authors found that polyhydramnios, which was present overall in 40% of pregnancies, was associated with favorable fetal outcomes (50% of women with favorable fetal outcomes had polyhydramnios vs. 14.3% of women with adverse outcomes; \( P = 0.03 \)). A subsequent study from Canada that used an intensive nocturnal dialysis regimen found a similar fetal survival rate of 86.4% in women who received an average of 43 ± 6 hours of dialysis per week. However, there were important differences between the 2 studies. First, the average gestational age at delivery in the Canadian cohort was later, at 36 weeks, compared with 32.7 weeks in the Luders et al. cohort. Second, there was a lower incidence of polyhydramnios in the Canadian cohort (only 1 of 22 pregnancies). Polyhydramnios in pregnant dialysis patients is believed to be due to solute diuresis in the fetus because of elevated maternal urea levels. Therefore, the decreased incidence of polyhydramnios in the Canadian cohort might reflect increased solute clearance due to more intensive dialysis.

The substantial difference in gestational ages at delivery beg the question of whether all pregnant women on dialysis should be treated with prolonged dialysis therapy times, in excess of 36 hours/week, to achieve more successful pregnancy outcomes. With this question in mind, Luders et al. presented their experience with an additional 59 pregnancies, which they combined with 34 pregnancies from their previous publication. Women received dialysis 6 times per week, with a high-flux dialyzer, a blood flow rate of 350 ml/min, and a dialysate flow of 800 ml/min. Women with diuresis of >1000 ml/d, who were on dialysis <1 year, or with a body weight <70 kg were assigned 1.5 to 2.0 hours per session, and all others were assigned 2.0 to 3.0 hours per session. The dialysis regimen was lengthened based on the need to maintain solute balance.
on clinical markers, such as hypertension, anorexia, nausea, excessive weight gain, and polyhydramnios. In the latter portion of the study period, the session was also lengthened to maintain a mid-week BUN level of <35 mg/dl, based on findings from their previous study. All women received aspirin and calcium supplementation, and were followed by a multidisciplinary team that included nephrologists, obstetricians, nutritionists, and neonatologists.

The average time on dialysis was similar to their previous study, with women on dialysis for an average of 2.6 ± 0.7 h/d and 15.4 ± 4 h/wk. Including the contribution of residual kidney function, the mean weekly standard Kt/V was 4.3 ± 0.8, and the average mid-week BUN level was 36.9 ± 9.4 mg/dl. The successful delivery rate was 89.2%. The average gestational age at delivery was better than that previously reported at 35 weeks (range: 25–39 weeks). There were 10 perinatal deaths (11%), and 70% of babies had a neonatal intensive care unit admission. Preeclampsia, which was present in 13 of 93 (14%) pregnancies, was again associated with adverse fetal outcomes. This relatively low rate of preeclampsia (in light of the high risk in advanced renal disease) was likely due to several factors, including the difficulty in diagnosing preeclampsia in dialysis patients, as well as the routine practice of inducing delivery at 37 weeks’ gestation in this cohort, after which more women might have developed preeclampsia. The only variable that correlated with preeclampsia was residual diuresis volume. In multivariable linear regression models, preeclampsia and average BUN level were negatively associated with birth weight, whereas polyhydramnios, hours per week on dialysis, and diuresis volume were all positively associated with birth weight (Figure 1).

This study demonstrated that although the dialysis dose and BUN are critically important to pregnancy outcomes, placental integrity is still a significant determinant of fetal outcomes. Preeclampsia and polyhydramnios might represent opposite ends of the placental perfusion spectrum. Placental hypoperfusion and ischemia could lead to an imbalance in angiogenic factors, and, ultimately, the systemic syndrome of preeclampsia. Women with advanced chronic kidney disease have endothelial dysfunction, increased oxidative stress, and systemic inflammation that might predispose to abnormal placentation, which increases the risk of intrauterine growth restriction and preeclampsia. In contrast, in the setting of adequate placenta perfusion, there is increased delivery of maternal solute to the fetus, which results in the clinical finding of polyhydramnios. In this study, the association of polyhydramnios and adverse fetal outcomes remained significant even after adjusting for therapy times and mid-week BUN level.

Polyhydramnios might therefore be a surrogate marker of placental perfusion in pregnant dialysis patients in the same way that intrauterine growth restriction might herald the development of preeclampsia.

Another notable finding in this study was that higher residual renal function was associated with a decreased risk of preeclampsia. The authors pointed out that more intensive dialysis was associated with a faster decline in residual kidney function. Does more intensive dialysis in pregnancy paradoxically increase the risk of preeclampsia by decreasing residual function? So far, there is no evidence to support this because the rates of preeclampsia and other markers of placental insufficiency in the Canadian cohort were similar to the Brazilian cohort (~13%) despite intensive dialysis therapy. However, without a gold standard diagnostic test for preeclampsia in women on dialysis, this question will remain difficult to answer.

Finally, this study demonstrated that less therapy time and an individualized dialysis dosing strategy aimed at achieving a mid-week BUN of 35 mg/dl could be effective in

![Figure 1. Summary of risk factors associated with adverse fetal outcomes in the Luders et al. study. BUN, blood urea nitrogen.](image-url)
pregnant dialysis patients. Many providers might not be able to provide nocturnal therapies with long dialysis times, and there might also be other complications of such intensive dialysis, including nutritional deficiencies, hypophosphatemia, and access fatigue, that might tip the scales back to less intensive therapy if fetal outcomes are comparable.

The improving fetal outcomes in pregnant dialysis patients are staggering when viewed in the historical context. The fact that there is a debate over the optimal dialysis dose to improve the already excellent fetal survival rates and average gestational age at delivery is an accomplishment in and of itself. Part of this success is undoubtedly due to advances in neonatal care. Long-term data on how babies born to women on dialysis progress into adulthood, from a physical and cognitive standpoint, are badly needed, but will take many more decades to accumulate. In the meantime, this series adds important information to this body of literature, giving providers more comfort that what once was considered incredible is now possible with the appropriate care.

**DISCLOSURE**

The author declared no competing interests.

**REFERENCES**

1. Luders C, Titan SM, Kahhale S, et al. Risk factors for adverse fetal outcome in hemodialysis pregnant women. Kidney Int Reports. 2018;3:1077–1088.
2. Hou SH. Frequency and outcome of pregnancy in women on dialysis. Am J Kidney Dis. 1994;23:60–63.
3. Asamiya Y, Otsubo S, Matsuda Y, et al. The importance of low blood urea nitrogen levels in pregnant patients undergoing hemodialysis to optimize birth weight and gestational age. Kidney Int. 2009;75:1217–1222.
4. Luders C, Castro MC, Titan SM, et al. Obstetric outcome in pregnant women on long-term dialysis: a case series. Am J Kidney Dis. 2010;56:77–85.
5. Hladunewich MA, Hou S, Odutayo A, et al. Intensive hemodialysis associates with improved pregnancy outcomes: a Canadian and United States cohort comparison. J Am Soc Nephrol. 2014;25:1103–1109.