Clinical Use of Angiogenic Factors in Managing a Pregnant Woman on Hemodialysis to Term

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INTRODUCTION

Women with chronic kidney disease (CKD) have a 10-fold increased risk of superimposed preeclampsia compared with women without CKD.\textsuperscript{1} Superimposed preeclampsia affects up to 60% of women with CKD, and the resulting iatrogenic preterm delivery is reported to occur in up to 80% of pregnant women on dialysis.\textsuperscript{1} However, the accuracy of the diagnosis is challenged by the clinical diagnostic criteria\textsuperscript{2} as accelerated hypertension and proteinuria in women with CKD are often indistinguishable from pregnancy-related maternal physiological changes. Angiogenic factors, soluble fms-like tyrosine kinase-1 (sFlt1) and placental growth factor (PlGF), have been found to be useful in predicting and diagnosing preeclampsia, particularly in women with underlying chronic hypertension and CKD, in whom clinical diagnosis is challenging.\textsuperscript{3} However, the clinical use of angiogenic markers in pregnant women on dialysis for predicting and diagnosing preeclampsia has not been adequately explored. We present a case and a review of the literature of angiogenic markers in pregnant patients on dialysis. A nulliparous woman commenced hemodialysis in her second trimester and successfully underwent a planned induction of labor at 37$^{+1}$ weeks of gestation despite accelerating hypertension, with close monitoring of angiogenic factors. To our knowledge, this is the first case report that reveals the use of angiogenic markers in guiding clinicians in temporizing pregnancy in a patient on dialysis.

CASE PRESENTATION

A 34-year-old nulliparous nonsmoker with stage 3BCKD owing to pauci-immune glomerulonephritis had serum creatinine, urea, albumin, and urinary protein excretion of 170 $\mu$mol/l, 13.2 mmol/l, 32 g/l, and 2.8 g/d, respectively, at conception. She received 6 months of intravenous cyclophosphamide 2 years before conception, following which she received oral mycophenolic acid 1 g 12-hourly until 12 months before conception. She was not on immunosuppressants at conception.

She was commenced on aspirin 100 mg and calcium 1200 mg daily at 10 weeks of gestation, in addition to multivitamins for pregnancy, labetalol 50 mg 8-hourly for hypertension and thyroxine 50 mcg daily for subclinical hypothyroidism. After close fortnightly biochemistry assessment, she was commenced on hemodialysis via a right internal, jugular, tunneled vascular catheter at 17 weeks of gestation owing to a progressive rise in serum urea and creatinine to 15 mmol/l and 200 $\mu$mol/l, respectively.

Fixed sodium, bicarbonate, and calcium dialysate concentrations of 135 mmol/l, 24 mmol/l, and 1.25 mmol/l, respectively, with a dialysate pump flow of 500 ml/min were used through the duration of her pregnancy. The dialysate potassium concentration (2.0–3.0 mmol/l) was adjusted based on the predialysis serum potassium level to maintain a target of 3.5–4.0 mmol/l. Serum albumin was maintained between 19 and 22 g/l by an incremental high-protein diet of 1.8–2 g/kg per day.
| Gestation | Pre-HD BP | Post- HD BP | Dose of labetalol | Duration (h) | UF (ml) | Frequency a wk (d) | sFlt1 pre-HD (pg/mmol) | sFlt1 post- HD (pg/mmol) | sFlt1 range for gestation (pg/mmol) | PlGF pre-HD (pg/mmol) | PlGF post-HD (pg/mmol) | PlGF range for gestation (pg/mmol) | Ratio pre-HD | Ratio post-HD | EFW (g) | Umbilical artery PI |
|-----------|-----------|-------------|-------------------|--------------|--------|-------------------|------------------------|------------------------|-----------------------------------|-------------------|-------------------|-------------------------------|-------------|-------------|--------|-------------------|
| 22 wk 3 d | 129/70    | 129/80      | 50 mg TDS         | 5            | Nil    | 3                 | 1014                   | 5104                   | 572–2997                          | 706               | 932               | 119–605                       | <1          | 5           | 415    | 1.01              |
| 23 wk 3 d | 134/77    | 135/82      | 100 mg TDS        | 5            | Nil    | 3                 | 2710                   | 5197                   | 572–2997                          | 1020              | 1225              | 119–605                       | <1          | 4           | 785    | 1.06              |
| 24 wk 3 d | 138/73    | 138/73      | 100 mg TDS        | 6            | Nil    | 3                 | 795                    | 618–3205               | 618–3205                          | 708               | 169–1117                     | <1               |              |        |                   |
| 25 wk 6 d | 121/62    | 121/62      | 100 mg TDS        | 5            | Nil    | 3                 | 931                    | 618–3205               | 618–3205                          | 648               | 169–1117                     | <1               |              |        |                   |
| 26 wk 6 d | 130/72    | 134/83      | 100 mg TDS        | 5            | Nil    | 3                 | 950                    | 618–3205               | 618–3205                          | 1118              | 169–1117                     | <1               |              |        |                   |
| 27 wk 6 d | 149/100   | 140/80      | 200 mg TDS        | 5.5          | Nil    | 5                 | 955                    | 618–3205               | 618–3205                          | 1052              | 169–1117                     | <1               |              |        |                   |
| 28 wk 6 d | 134/70    | 139/73      | 200 mg TDS        | 5.5          | Nil    | 5                 | 1202                   | 618–3205               | 618–3205                          | 734               | 169–1117                     | 2                |              |        |                   |
| 29 wk 6 d | 154/94    | 142/80      | 300 mg TDS        | 5.5          | 200    | 5                 | 3870                   | 773–5165               | 773–5165                          | 734               | 114–1297                     | 6                |              |        |                   |
| 30 wk 6 d | 144/78    | 134/80      | 300 mg TDS        | 5.5          | 200    | 5                 | 1257                   | 773–5165               | 773–5165                          | 585               | 114–1297                     | 2                |              |        |                   |
| 31 wk 6 d | 145/81    | 142/86      | 300 mg TDS        | 5.5          | 200    | 5                 | 1452                   | 773–5165               | 773–5165                          | 637               | 114–1297                     | 1                |              |        |                   |
| 32 wk 6 d | 152/100   | 140/82      | 400 mg QID        | 5.5          | 300    | 6                 | 1766                   | 773–5165               | 773–5165                          | 711               | 114–1297                     | 2                |              |        |                   |
| 33 wk 2 d | 146/87    | 140/70      | 400 mg QID        | 6            | 300    | 6                 | 3887                   | 773–5165               | 773–5165                          | 437               | 114–1297                     | 9                |              |        |                   |
| 34 wk 6 d | 148/82    | 138/78      | 400 mg QID        | 6            | 600    | 6                 | 2461                   | 992–7363               | 992–7363                          | 433               | 78–984                      | 6                |              |        |                   |
| 36 wk 4 d | 154/94    | 142/80      | 400 mg QID        | 6            | 1000   | 6                 | 3878                   | 992–7363               | 992–7363                          | 226               | 78–984                      | 17               |              |        |                   |
| 37 wk 1 d | 142/76    | 144/78      | 400 mg QID        | 6            | 1000   | 6                 | 4127                   | 1533–9184             | 1533–9184                          | 158               | 54–862                      | 26               |              |        |                   |

BP, blood pressure; DBP, diastolic blood pressure; EFW, estimated fetal weight; HD, hemodialysis; mg, milligram; PI, pulsatility index; PlGF, placental growth factor; PP, postpartum; QID, quarter in die (4 times a day); SBP, systolic blood pressure; sFlt1, soluble fms-like tyrosine kinase; TDS, ter die sumendus (3 times a day); UF, ultrafiltration.

*Based on Verlohren et al.4

*A ratio of ≤38 was used to rule out superimposed preeclampsia.

*Hydralazine 25 mg 6-hourly added as antihypertensive.

*Day of planned induction of labor.

*Dialysis ceased.
Hemoglobin concentration was maintained between 110 and 120 g/l with regular and incremental doses and frequency of epoetin alfa and fortnightly iron polymaltose infusions (200 mg) to target and maintain a transferrin saturation of 20%–30%. Unfractionated heparin (loading dose of 1000 IU and an infusion rate of 1000 IU/h) was administered with each dialysis session. An FX-80 (Fresenius Medical Care Asia Pacific, Sydney, Australia) dialyzer was used through the duration of pregnancy.

Weekly predialysis biochemistry that included angiogenic factors (sFlt1 and PlGF), fortnightly sonographic fetal assessment, cervical length, and uteroplacental flows was performed (Table 1). Two, oral, 75 g glucose tolerance tests, at 12 and 26 weeks of gestation, did not reveal gestational diabetes. A short cervical length was noted at 18 weeks of gestation, and 200 mg progesterone was vaginally commenced and subsequently ceased at 36 weeks of gestation. Dialysis frequency, duration, blood pump flow, and ultrafiltration were incrementally increased to target and maintain predialysis serum urea of <12 mmol/l and postdialysis blood pressure of 145/95 mm Hg (Table 1).

At 27+6 weeks of gestation, her hypertension worsened (149/100 mm Hg) along with an increase in pedal edema in the absence of neurologic symptoms, liver function, or platelet count abnormalities. sFlt1/PlGF ratio was normal, and the estimated fetal weight was at 50th centile along with normal umbilical artery flows (Table 1). Given the absence of features of placental dysfunction, her hypertension was managed with increased labetalol (200 mg 8-hourly) to target a postdialysis systolic blood pressure of 135–145 mm Hg and diastolic blood pressure of 85–95 mm Hg.

From the 29+6 to 36+4 weeks of gestation, her blood pressure gradually increased, once again in the absence of other signs or symptoms of placental dysfunction (Table 1). Weekly sFlt1/PlGF assessment and fortnightly sonographic assessment (Table 1) confirmed the absence of features of placental dysfunction. Given this, her hypertension was managed with incremental changes to antihypertensives and the dialysis prescription (Table 1).

As planned, at 37+1 weeks of gestation, she underwent induction of labor and vaginally delivered a healthy male newborn with a birthweight of 2515 g (14th centile) who did not require neonatal intensive care unit admission. At the time of induction, she was on labetalol 400 mg and hydralazine 25 mg 6-hourly and slow-release nifedipine 30 mg 12-hourly. She breastfed her newborn and used heparin 5000 IU 12-hourly, subcutaneously, postpartum for prophylaxis against deep venous thrombosis. She is currently being followed up for long-term dialysis planning and transplant assessment.

**DISCUSSION**

To our knowledge, this is the first case report that documents the use of the real-time, clinically validated, sFlt1/PlGF ratio in ruling out superimposed preeclampsia in a pregnant woman on dialysis, allowing for term delivery. Our case illustrates the clinical use of real-time angiogenic factor assessment in ruling out superimposed preeclampsia in a pregnant woman on dialysis, whose worsening hypertension and edema would have otherwise suggested the need for preterm delivery.

Placental angiogenic factors, sFlt1 and PlGF have been found to be abnormal, resulting in an elevated ratio 2–6 weeks preceding the clinical spectrum of preeclampsia. This is thought to be an early biochemical indication of placental dysfunction. Recent studies have revealed that the the sFlt1/PlGF ratio, with a cutoff ≤38, has a negative predictive value of 97.9% (66.2% sensitivity and 83.1% specificity) for 4 weeks from assessment. The use of sFlt1/PlGF ratio has been particularly useful in women with chronic hypertension and CKD in ruling out superimposed preeclampsia and allowing for temporization of pregnancy through medical management without the need to expedite delivery. However, the current literature on the use of this ratio in women on dialysis is sparse with only 4 case reports (Table 2).

Cornelis et al., Shan et al., and Akbari et al. have described women who delivered preterm, at 35+5, 29+2, and 35 weeks gestation, respectively, owing to maternal hypertension. These women did not have other accompanying clinical, biochemical, or sonographic features of placental dysfunction. In addition, where reported, these women were often on a single antihypertensive agent at the time of delivery. The newborns in the reports of Cornelis et al. and Shan et al. required ventilatory support in the neonatal intensive care unit for prematurity-related respiratory distress. Retrospective analysis of sFlt1 and PlGF in the reports of Cornelis et al. and Akbari et al. and that of sFlt1 and sEng in the report of Shan et al. were not indicative of preeclampsia at the time of hypertension, suggesting the possibility of an
## Table 2. A comparison of the maternal, newborn, and angiogenic factors in the literature

| Authors             | Gestation at which dialysis was commenced | Type of RRT | Gestation of delivery | BP before delivery | Antihypertensives at time of delivery | Magnesium infusion | Other clinical features of preeclampsia | Indication for delivery | Newborn weight (g) and centile | NICU support required for newborn | Placental histopathology | Type of angiogenic assay used | Did angiogenic factors rule out preeclampsia |
|---------------------|------------------------------------------|-------------|-----------------------|--------------------|---------------------------------------|-------------------|----------------------------------------|-------------------------|-----------------------------------|--------------------------------|---------------------------|---------------------------|-------------------------------|---------------------------------|
| Shan et al.8 (2008) | Prepregnancy HD 32                      | 29–2       | 200/100               | Metoprolol 50 mg   | No                                    | No                | Maternal hypertension                 | 1325 (50th)             | Yes                               | Normal                        | R&D ELISA (sFlt1 and sEng)     | Yes—retrospectively           |                               |
| Cornelis et al.7 (2013) | 26 HD 35                                | Not specified | No                      | Magnesium infusion | Yes                                   | Normal            | Maternal hypertension                 | 2480 (22nd)             | No                               | Not specified                 | Clinically validated Cobas/Elecsys human sFlt1 and PlGF automated system | Yes—retrospectively           |                               |
| Akbari et al.9 (2016) | Prepregnancy HD 33                      | 170/102    | Labelator 200 mg QID  | No                  | No                                    | Maternal hypertension | 2012 (14th)             | Normal                      | R&D ELISA (sFlt1 and PlGF)     | Indeterminate owing to variation in cutoff value |                               |
| Morisawa et al.8 (2019) | Prepregnancy HD 33+6                   | >180       | Labetalol 100 mg QID  | No                  | No                                    | Maternal hypertension | 2138 (86th)             | Not specified              | R&D ELISA (sFlt1 and PlGF)     |                               |                               |
| Shanmugalingam et al.8 (2020) | 17 HD 37–1                           | 144/78     | Labetalol 400 mg and hydralazine 25 mg QID | No | Planned induction at term | 2515 (14th)             | No                               | Normal                      | Clinically validated Cobas/Elecsys human sFlt1 and PlGF automated system | Yes—prospectively              |                               |

BP, blood pressure; ELISA, enzyme-linked immunosorbent assay; HD, hemodialysis; NICU, neonatal intensive care unit; PlGF, placental growth factor; QID, quater in die (4 times a day); RRT, renal replacement therapy; sEng, soluble endoglin; sFlt1, fms-like soluble tyrosine kinase.

CONCLUSION

We, therefore, conclude that the use of the clinically validated sFlt1/PlGF ratio is beneficial in ruling out superimposed preeclampsia in pregnant women on dialysis and in minimizing the risk of intrageneic premature delivery. As reported in our report and also by Cornelis et al., indicated that the absence of these angiogenic factors in the dialysate of our patient, indicating that these angiogenic factors are not cleared through dialysis. The lack of clinically significant change in the sFlt1/PlGF ratio with dialysis, as reported by Morisawa et al., indicates that the sFlt1/PlGF ratio can be assessed independent of the time of dialysis.

All the authors declared no competing interests.

PATIENT CONSENT

Informed written consent was obtained from the patient.

DISCLOSURE

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DISCLOSURE

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|---------|------------------------------------------|-------------|-----------------------|--------------------|---------------------------------------|-------------------|----------------------------------------|-------------------------|-----------------------------------|--------------------------------|---------------------------|---------------------------|-------------------------------|---------------------------------|
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| Cornelis et al.7 (2013) | 26 HD 35                                | Not specified | No                      | Magnesium infusion | Yes                                   | Normal            | Maternal hypertension                 | 2480 (22nd)             | No                               | Not specified                 | Clinically validated Cobas/Elecsys human sFlt1 and PlGF automated system | Yes—retrospectively           |                               |
| Akbari et al.9 (2016) | Prepregnancy HD 33                      | 170/102    | Labelator 200 mg QID  | No                  | No                                    | Maternal hypertension | 2012 (14th)             | Normal                      | R&D ELISA (sFlt1 and PlGF)     | Indeterminate owing to variation in cutoff value |                               |
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| Shanmugalingam et al.8 (2020) | 17 HD 37–1                           | 144/78     | Labetalol 400 mg and hydralazine 25 mg QID | No | Planned induction at term | 2515 (14th)             | No                               | Normal                      | Clinically validated Cobas/Elecsys human sFlt1 and PlGF automated system | Yes—prospectively              |                               |
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SUPPLEMENTARY MATERIAL
Supplementary File (PDF)
Supplementary References.
Table S1. Teaching points.

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