Pregnancy in Dialysis Patients: Two Successful Cases from a Saudi Renal Center and Management Guidelines

Khalid AL-Saran, Alaa Sabry

Prince Salman Center for Kidney Diseases, Riyadh, Kingdom of Saudi Arabia

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Correspondence:
Dr. Al-Saran
Tel: 00966505260952
Fax:0096614975533
E.mail:khalid_aln@yahoo.co.uk

ABSTRACT

Fertility is markedly reduced in potients with chronic renal failure. Wi here by repord two cases of seccuessful prengnancy in 2 Saudi patienst, the first with chronic renal failure on chronic hemodialysis and the second with pre-existing renal disease aggravated by pregnancy.

Keywords: Pregnancy, dialysis, chronic renal failure.

INTRODUCTION

Fertility is markedly reduced in patients with chronic renal failure. For women with pre-existing renal disease, pregnancy is associated with increased rate of fetal complications and considerable risk of renal disease progression (1). Due to substantial improvement in the antenatal and neonatal care, the fetal outcome has improved considerably in the last two decades (2).

In the saudi society, the result of a survey concerned with the frequency of pregnancy reported an incidence of 7% over five years period (1.4 per year) in end stage renal disease (ESRD) women undergoing regular hemodialysis, which may reflect the cultural endorsement of having offspring (3,4). In 2005 Malik GH et al (5) reported a yearly frequency of 0.66 in female patients on maintenance hemodialysis and none on chronic peritoneal dialysis. We hereby report 2 cases of successful pregnancy managed at the Prince Salman Center for Kidney Diseases (PSCKD).

Case 1

A 37 year old Saudi female, 8th gravida with history of a single 2nd trimester abortion with six living offsprings. The patient was started on regular hemodialysis at PSCKD in January 2006. Three months after maintenance hemodialysis, she was presented with abdominal distension and 4 weeks of amenorrhea. She was found

to be pregnant following a blood test, which was confirmed by a pelvi-abdominal ultrasonography. Her dialysis prescription consisted of 3 extended weekly sessions due to her refusal of daily dialysis (7 hours each with a dialysate flow rate of 800 ml/min). Her eKt/V was between 3 to 3.7 (she was passing 400 mL urine/day with estimated GFR of 4.9 mL/min/1.73 m^2). Her normalized protein catabolic rate (nPCR) was 1.46, Blood gas analysis revealed ph of 7.36 and HCO_3 of 24.2, serum calcium 2.26 mmol/L and serum phosphate 1.17 mmol/L. Programmed adjustment of the dry weight was done by revising the estimated dry weight weekly to an expected weight gain during progression of pregnancy, in discussion with the obstetric team. Her medications consisted of; Erythropoietin, which its dose was increased from a mean weekly dose of 8000 units to 14000 units during pregnancy (to maintain a hemoglobin level of 10 gm/dl). Iron requirement was also increased from oral ferrous fumarate (100 mg/day) to IV iron saccharate (100 mg/weekly). She also received Calcium carbonate 1500 mg/day as phosphate binder, multivitamins and folic acid. Her mean pre-dialysis blood urea nitrogen (BUN) was 15.13 mg/dl.The blood pressure was controlled without antihypertensive medication. On the 30th week of pregnancy she had a pre-term vaginal delivery of a viable premature baby weighing 2.3 kg who had an uneventful neonatal period.

Case 2

A 36 year old female patient, 9th gravida with 4 living offsprings and four abortions who had a history suggestive of chronic glomerulonephritis. Her first pregnancy was complicated by pre-eclampsia, nevertheless it was completed successfully, and the following 3 successful pregnancies were uncomplicated.

During the first trimester of her 9th pregnancy (March 2006), she developed lower limb oedema and felt unwell with persistent nausea and vomiting. Her urinalysis revealed proteinuria (3+) and her biochemical investigations revealed high plasma creatinine (15.56 mg/dL) and BUN (74 mg/dl) values and diagnosed as end stage renal disease (ESRD). Renal biopsy was not done in view of the history of chronic glomerulonephritis and patient's refusal. She was maintained on hemodialysis (HD) since that time. She was transferred for HD in our center at the 20th week of gestation. The dose of dialysis was increased to 6 hours daily HD sessions a week.

A eKt/V of 2 was achieved (she was passing 350 ml urine/day with estimated GFR of 4.07 ml/min/1.73 $m^{2)}$ and a mean pre-dialysis BUN of 12.65 mg/dl. Her nPCR was 1.24, Blood gas analysis revealed ph of 7.35 and HCO3 of 23.1, serum calcium 2.23 mmol/L and serum phosphate 1.52 mmol/L. Programmed adjustment of the dry weight was done by revising the estimated dry weight weekly to an expected weight gain during progression of pregnancy, in discussion with the obstetric team. Her medications consisted of; α methyl dopa (500 mg TID - with dose adjustment when necessary for tight BP control: below 120/80 mmHg), folic acid 5mg OD, Calcium carbonate (600 mg TID). As expected, erythropoietin and iron requirements were increased during her pregnancy (Erythropoietin from a weekly dose of 6000 to a mean of 14000 units), Iron saccharate (100 mg IV once every week) instead of 100 mg/day of oral ferrous fumarate. Her serum albumin ranged between 2.8 and 3 gm/dl and her hemoglobin ranged between 8.33 and 9.74 g/dl.

In both cases, in addition to routine pregnancy care, fetal well-being was monitored by way of serial ultrasound assessment of biophysical profiles, doppler studies, and estimated fetal weights. At 32nd week's gestation the patient's blood pressure increased despite an increasing dose of α-methyldopa and she developed proteinuria. A diagnosis of pre-eclampsia necessitated a cesarean section that resulted in a single viable girl weighing 1.7 kg who had an uneventful neonatal period.

DISCUSSION

The incidence of pregnancy and successful outcome in patient on dialysis has increased in recent years. However, fetal and maternal morbidity remain significant (6).

In 1971 Confortini et al. (7) reported the first successful pregnancy in a woman on chronic hemodialysis HD.

In 1980, the European Dialysis and Transplant Association (EDTA) reported a pregnancy incidence of 0.9% (8). Recent publications report pregnancy in 1–7% in women on chronic dialysis (9,10). Moreover, pregnancy in contemporary women on dialysis is more likely to be successful, with 30–50% of pregnancies resulting in delivery of surviving infant (11, 12).

The results of a survey of pregnancy in the HD popu-

lation in the Kingdom of Saudi Arabia over 5 years (1985 to 1990) showed a frequency of 7% (27 among 380 women on HD) with 37% successful outcome (10 patients had successful outcome) (3).

Compared with reports from the 1980s, regular menstrual periods are more often noted by contemporary premenopausal women on dialysis (13). The effects of improved dialysis and anemia management on the ability to conceive could increase the likelihood of conception in dialysis patients and thus the reported incidence of pregnancy.

Early diagnosis of pregnancy in ESRD requires careful attention as irregular menses, amenorrhea and nausea are common in this group and elevated beta-subunit of human chorionic gonadotropin has been observed in some patients with renal failure which may give a false-positive pregnancy test while late diagnosis delays the intensive antenatal care and reduce the successful outcome (1).

In one of our cases, these symptoms were first attributed to inefficient dialysis before pregnancy was diagnosed, as urine testing for pregnancy is not reliable. As recommended, we used abdominal sonography to confirm pregnancy and assess gestational age as soon as we were informed about the pregnancy. Therefore, in such cases we suggest a blood pregnancy test [to estimate B subunit of

human chorionic gonadotrophin (HCG) in blood] to be done prior to any abdominal x-ray if there an abdominal complaint.

The number of successful pregnancies in dialysis patients has improved over the years (14). The outcome is better in patients who conceived before starting dialysis compared with those who became pregnant while on dialysis (11). An increase in the congenital anomalies is also documented in pregnancies on dialysis (11).

In our view, these figures should be interpreted with caution for a number of reasons. Firstly, there are no comprehensive prospective studies of conception among women with ESRD. Secondly, the literature addressing pregnancy in women on dialysis is composed primarily of survey studies, single center retrospective reviews, and case reports. Thirdly, pregnancies ending in the first or second trimester by elective or spontaneous abortions are variably included. Thus reporting bias may confound the results.

Since 1980s, the infant survival rate has improved from 20-30% (15) up to 50% in 2003 (10). This improved infant survival rate is probably due to the care provided by a multidisciplinary management team, characterized by close collaboration between patients, nephrologists, dialysis staff, obstetricians, and neonatologists.

Despite improved infant survival, half of pregnancies in women on dialysis are not successful; the proportion of neonatal deaths remains higher than in the general population. Infants born to women on dialysis are usually premature, with an average gestational age of 32 weeks. Although these infants typically weigh less than 2000 gram, birth weights correspond to gestational age and thus intrauterine growth retardation does not appear to be more common than in the general population (15). On the hand the National Registry of Pregnancy in Dialysis Patients reported that 36%of infants born to women who conceived after starting dialysis weighted less than 1500 gram at birth and 28% were small for gestational age (8). Our cases are in agreement with earlier reports regarding gestational age as we also failed to prolong gestational age beyond 32 weeks, despite the maximum multidisciplinary care we tried to provide.

Multiple causes of premature delivery exist, including polyhydramnios, maternal hypertension, and premature rupture of the membranes (14). Polyhydramnios which has been postulated to occur in response to the high placental BUN concentration and fetal solute diuresis, giving rise to excessive amniotic fluid accumulation (16). Since increasing dialysis frequency lowers predialysis BUN levels, adequate dialysis may reduce the occurrence of polyhydramnios and thus lower the risk of premature labor (1). Increasing the dialysis dose prolongs gestation, resulting in a higher infant birth weight and thus an infant with better chance of survival (3,17).

Despite the fact that no randomized prospective trials of pregnant women on dialysis exist, retrospective data suggest maintaining predialysis BUN values at ≤ 50 mg/dl is an appropriate goal (16,18). Beyond 16 to 20 weeks, the dialysis dose will probably need to be increased in order to maintain a predialysis BUN ≤50 mg/dl. Pregnant women on dialysis will generally require 16–24 hours of HD each week. Due to the potential for fetal malformations with formaldehyde

or ethylene oxide exposure, biocompatible, non-reuse dialyzers are recommended (19).

In one series, fetal mortality was directly proportional to maternal blood urea nitrogen level, with no successful pregnancies occurring in patients with BUN greater than 60 mg/dL (10). In our two cases the mean pre-dialysis BUN was maintained at (15.13 mg/dl and 12.65 respectively) during pregnancy which may contributed in part to the successful outcome.

In the largest study to date, the Registry for Pregnancy in Dialysis Patients reported a significant correlation between hours spent on dialysis therapy and improved fetal outcome. The increase in dialysis time seems to improve the pregnancy outcome and offer several advantages: It ensures less uremic environment to the fetus and allows the mother more liberal diet (Potassium and protein), it may help to control hypertension and fluid intake and may also reduce the amplitude of blood voulme and electrolyte shifts (21). This is consistent with our results as in both cases dialysis treatment was intensified (up to daily dialysis in case 2) resulting in viable mature babies.

In addition to the effects on fetal birth weight and the development of polyhydramnios, more frequent dialysis is likely to minimize shifts in maternal intravascular volume. By maintaining lower

ultrafiltration goals per treatment, episodes of maternal hypotension during dialysis can be minimized and compromised fetoplacental blood flow avoided. Stable maternal hemodynamics may also contribute to longer gestation. Estimating appropriate target weights for pregnant women on dialysis may be difficult. Allowances must be made for fetal and placental growth as well as the 30% increase in plasma volume that occurs with pregnancy. After the first trimester, weight gain is usually linear and is approximately 1 pound/week (21). Ultrafiltration goals can be adjusted based on this expected pregnancy-induced weight gain. Maternal diastolic blood pressure should be maintained in the 80–90 mmHg range (20).

Similarly dialysate adjustment may be needed to maintain appropriate levels of serum calcium and to avoid hypocalcemia and/or post-treatment hypercalcemia (19). Since the placenta converts some 25-hydroxyvitamin D3 to 1, 25-dihydroxyvitamin D3, adjustment of vitamin D may be required during pregnancy and should be guided by measurement of levels of vitamin D, parathyroid hormone, calcium and phosphorus (22). Because dialysis frequency is increased during pregnancy, a higher dialysate potassium concentration will usually be required to avoid hypokalemia.

Anemia occurs during pregnancy and pregnant dialysis patients require intensive anemia management. Erythropoietin has been given safely to pregnant dialysis patients (21). Erythropoietin doses need to be increased by approximately 50% in order to maintain target hemoglobin levels of 10–11 g/dl. The reason for the higher erythropoietin doses is unknown, but pregnancy-induced increased vascular volume with subsequent hemodilution and possibly erythropoietin resistance due to enhanced cytokine production during pregnancy may contribute (22). A target hematocrit between 30 and 35 was recommended (20). Observational studies suggest that maternal erythropoietin does not cross the placental barrier and do not directly affect the fetus (23). This is consistent with our results, as Erythropoietin doses were increased (by more than 70% and 100% in case 1 and 2 respectively) to maintain hemoglobin level comparable to that before pregnancy.

In addition, frequent monitoring of iron stores is also required during pregnancy. Intravenous iron appears to be safe (1,21,23). Therefore, Grossman et al. (23) recommended an IV 500 mg dose of iron, administered as soon as pregnancy is diagnosed if transferin saturation is less than 30%.

Low-dose aspirin to prevent preeclampsia was suggested (19), and although heparin appears to be safe during pregnancy, minimizing the dose is recommended (19,20).

Hypertension is the most frequently reported maternal complication in this population, occurring in 42–80% of these women (9,20). Because maternal hypertension is associated with at least half of the cases of obstetric hemorrhage, abruptio placentae, and anemia, pregnant women on dialysis are more likely to experience these complications. However, such complications are rarely reported (3,23). Antihypertensive medications are often required and the mainstays of treatment are methyldopa, B-blockers, and hydralazine. In cases of severe hypertension, clonidine and calcium channel blockers have been used safely (19-23). In one of our cases, hypertension was difficult to

control after 30 weeks of gestation despite maximum dose of methyldopa, necessitating elective termination. However, the other case remained normotensive without any antihypertensive medications throughout pregnancy after intensified dialysis.

There is little information on the nutritional status of pregnant dialysis patients, but 1 g/kg/day protein intake plus an additional 20 g/day for fetal development has been suggested (17,18,24). Giatras et al (20) suggested additional protein intake for fetal development up to 1.8 g/kg/day. Folate supplementation is required, particularly early in fetal development. Replacement of water-soluble vitamins should be continued during pregnancy (17).

Maternal mortality is very low and rarely reported (3,11). Cesarean section delivery is common among women on dialysis and is most often prompted by premature rupture of membranes.

In summary, we hereby report two cases of successful pregnancy in 2 saudi patients, the first with chronic renal failure on chronic hemodialysis and the second with pre-existing renal disease aggravated by pregnancy.

We advise that all aspects of dialysis, including duration, adequacy, nutrition, anemia, calcium & phosphate metabolism and BP control need to be closely followed throughout the course of pregnancy. With careful monitoring and intensive hemodialysis, a successful outcome is possible. Furthermore, a successful pregnancy in woman on dialysis requires collaboration among nephrologists, dialysis unit staff and obstetricians. Finally, since pregnancy can occur in woman on dialysis, health care providers should discuss fertility and contraception with their premenopausal dialysis patients.

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