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Pregnancy in women undergoing hemodialysis: case series in a Southeast Brazilian reference center

Gestação em mulheres em tratamento hemodialítico: série de casos em um centro de referência do Sudeste do Brasil

Original Article

Keywords

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Palavras-chave

Gravidez de alto risco
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Abstract

PURPOSE: To describe maternal and neonatal outcomes in pregnant women undergoing hemodialysis in a referral center in Brazilian Southeast side. **METHODS:** Retrospective and descriptive study, with chart review of all pregnancies undergoing hemodialysis that were followed-up at an outpatient clinic of high-risk prenatal care in Southeast Brazil. **RESULTS:** Among the 16 women identified, 2 were excluded due to follow-up loss. In 14 women described, hypertension was the most frequent cause of chronic renal failure (half of cases). The majority (71.4%) had performed hemodialysis treatment for more than one year and all of them underwent 5 to 6 hemodialysis sessions per week. Eleven participants had chronic hypertension, 1 of which was also diabetic, and 6 of them were smokers. Regarding pregnancy complications, 1 of the hypertensive women developed malignant hypertension (with fetal growth restriction and preterm delivery at 29 weeks), 2 had acute pulmonary edema and 2 had *abruption placenta*. The mode of delivery was cesarean section in 9 women (64.3%). All neonates had Apgar score at five minutes above 7. **CONCLUSIONS:** To improve perinatal and maternal outcomes of women undergoing hemodialysis, it is important to ensure multidisciplinary approach in referral center, strict control of serum urea, hemoglobin and maternal blood pressure, as well as close monitoring of fetal well-being and maternal morbidities. Another important strategy is suitable guidance for contraception in these women.

Resumo

OBJETIVOS: Descrever os resultados maternos e neonatais de mulheres grávidas que estavam em tratamento de hemodiálise em um centro de referência no Sudeste brasileiro. **MÉTODOS:** Estudo retrospectivo e descritivo, com revisão de prontuários de todas as gestações em hemodiálise, acompanhadas no pré-natal especializado da região Sudeste do Brasil. **RESULTADOS:** Entre as 16 mulheres identificadas, 2 foram excluídas devido à perda de seguimento. Das 14 descritas, a hipertensão foi a causa mais frequente de insuficiência renal crônica (50% dos casos). A maioria (71,4%) realizava tratamento de hemodiálise há mais de um ano e todas elas foram submetidas a 5 ou 6 sessões por semana. Onze mulheres tinham hipertensão crônica, 1 das quais também era diabética, e 6 eram fumantes. Em relação às complicações da gravidez, 1 das mulheres hipertensas desenvolveu hipertensão maligna (com restrição de crescimento fetal e parto prematuro com 29 semanas), 2 tiveram edema pulmonar agudo e 2 apresentaram descolamento prematuro de placenta. O tipo de parto foi cesariana em 9 mulheres (64,3%). Todos os recém-nascidos tiveram Apgar aos cinco minutos maior que 7. **CONCLUSÕES:** Para melhorar os resultados perinatais e maternos de mulheres em hemodiálise, é importante ter uma abordagem multidisciplinar em centro de referência, um controle rigoroso da uremia, hemoglobina e pressão arterial materna, bem como acompanhar de perto o bem-estar fetal e a morbidade materna. Outra estratégia importante é a orientação adequada para contracepção nessas mulheres.

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Introduction

The chronic kidney disease (CKD) affects 3% of women of childbearing age¹. Pregnancy is a rare event in patients on dialysis due to hormonal alterations associated with its treatment and also low libido and high level of stress in the effected women.

However, changes in CKD therapy and advances in dialysis techniques have allowed an increase in fertility in these women over the last decades²⁻⁴, with a calculated frequency from 0.3 to 1.5% per year⁴. The rate of live births in this group also increased to 40-50%. Nevertheless, the neonatal mortality one remains high (8 to 13%)^{4,5}.

In Brazil, the main causes of CKD are hypertension and diabetes, which are also the primary causes of admissions to dialysis programs in developed countries. These diseases, and also glomerulonephritis, are amongst the three most frequent causes to CKD in Latin America⁶.

The first case report of pregnancy on a dialysis patient occurred in 1971 in a 35-year-old woman. Since then, other ones have been reported worldwide^{2,7}.

It is important to consider that pregnancy may also aggravate CKD⁸. Physiological changes such as increased progesterone levels and uterine growth lead to ureterocalyceal dilatation, greater urine stasis, and a higher chance of untreated asymptomatic bacteriuria and pyelonephritis that can have a significant impact on underlying CKD, worsening renal failure⁵.

Another functional alteration during pregnancy is a massive vasodilatation, resulting in decreased blood pressure and increased cardiac output, augmented plasma renal flow, and glomerular filtration rate (GFR), with a high excretion of glucose, amino acids, calcium, and protein². This urinary excretion of protein, although physiological, when complicated by underlying conditions, like hypertension and diabetes, can accelerate renal function loss in women with CKD².

Among the most significant maternofetal complications in women with CKD, there are the following: hypertension and preeclampsia (occurring in 80% of the cases)^{5,7,9}, anemia (with the need of blood transfusion), peritoneal infection, placental insufficiency, preterm labor, and stillbirth^{9,10}. Another risk of dialysis during pregnancy is the common occurrence of maternal hypotension throughout the procedure, which can cause poor placental perfusion and fetal distress³. Other fetal complications are: congenital anomalies (tetralogy of Fallot, genital changes), low birth weight (LBW), fetal growth restriction (FGR), polyhydramnios, prematurity (present in 84% of the cases)^{9,10}, electrolyte disturbance (hypocalcemia) due to osmotic diuresis⁵, and neonatal deaths^{9,10}.

In order to improve perinatal outcomes, several guidelines for renal replacement therapy and adequate follow-up have been developed: attention to pre-conception creatinine; precise indication of dialysis, with increased number of procedures during pregnancy (five to seven per week) targeting an urea level of 30–50 mg/dL^{5,7,8}; increased erythropoietin reposition with hemoglobin levels around 10–11 g/dL; severe control of electrolytes and blood pressure; prevention of urinary tract infection; and adequate fetal monitoring⁵. A multidisciplinary approach in a referral medical center is essential (i.e. with obstetrician, nephrologists, nutritionists)^{2,7}.

Understanding the scenario of this condition and improving techniques of renal replacement in these women are necessary to meet the increase cases worldwide and to define procedures for a favorable outcome.

This study aims to evaluate perinatal outcomes and maternal complications in pregnant women under dialysis in a Brazilian high-risk reference center.

Methods

We performed a retrospective chart review of a case series with pregnant women undergoing dialysis followed in the high-risk outpatient clinic of the State University of Campinas (Unicamp), over a ten-year period (2003–2012). Such center is the referral unit for a large catchment area and accounts for around 2,800 deliveries per year. High-risk pregnancies are followed-up receiving specialists' support, with written protocols for the conditions considered.

For this study, a specific form was created to retrieve clinical data from the medical chart of women who got pregnant under dialysis. The main investigator collected all information and then inserted data in an Excel (Excel 2) spreadsheet elaborated for this investigation. After consistency checking, further analyses were performed assuming a significance level of 5% and the software used was SAS, version 9.02.

Data were manually collected by the researchers through review of medical records, employing a form specifically created for this study. Later, they were put in an Excel 2 worksheet, also designed especially for this research.

Completed forms were appropriately filed to be accessible for quality control and identification of possible inconsistencies in the data. Review of the database was done to identify inconsistencies.

There was a 5% level of significance, and the software used for analysis was SAS, version 9:02. Variables considered included: maternal age, duration of pre-pregnancy dialysis, causes of CKD, number of prenatal visits, body mass index (BMI), number of previous pregnancies, use of anti-hypertensive medication during gestation,

maternal and fetal complications in pregnancy, mode of delivery, and neonatal outcomes.

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Results

Among the 16 women identified, 2 were excluded due to follow-up loss. In the remaining 14 ones with CKD who were undergoing dialysis, hypertension as probable etiology of CKD was seen in half (7) of the cases. Most women (71.4%) had been on dialysis for more than one year and all of them performed 5 to 6 hemodialysis sessions per week.

Other comorbidities included: 11 cases of hypertension, from which 1 subject had diabetes and 6 were current smokers. Five women had history of one previous Cesarean (C)-section (35.7%) and 3 had 2 or more (21.4%). Other data regarding characteristics of the participants are described in Table 1. The most widely

Table 1. Characteristics of women who became pregnant on hemodialysis

Characteristics	Means SD	
Age (years)	30.4	±5.4
Months in hemodialysis (pre-gestational)	23	±15.0
Number of visits during prenatal care	6.5	±3.6
Weight at the beginning of prenatal care	65.56	±12.26
Weight at the end of prenatal care	70.94	±14.76
n %		
Skin color (white)	10	(62.5)
Schooling (less than secondary school)	9	64.3
Not employed	11	73.3
BMI at first prenatal visit (kg/m ²)*		
Underweight	1	6.25
Normal weight	9	56.25
Overweight	5	31.25
Obesity	1	6.25
Number of pregnancies (including current)		
1	2	12.5
2	3	18.75
3 or more	11	68.75
Number of previous deliveries		
0	2	12.5
1	8	50.0
2 or more	6	37.5
Causes of chronic renal failure		
Hypertension	7	43.75
Glomerular disease	4	25.0
Pyelonephritis	1	6.25
Other causes	4	25.0
Antihypertensive treatment during pregnancy	12	75
Use of erythropoietin during pregnancy	8	53.3

*IOM (2009); BMI: body mass index.

used antihypertensive treatment was alpha-methyldopa (data not shown in table).

We evaluated gestational outcomes in the women who became pregnant while receiving hemodialysis treatment. One of them (the worst outcome in this series) developed malignant hypertension, with FGR and preterm delivery at 29 weeks for fetal distress. During pregnancy, two cases of *abruption placenta* occurred and two women had an acute pulmonary edema. The mode of delivery was C-section in 9 women (64.3%) and all of them chose to undergo tubal ligation at time of delivery. Cesarean indications were previous C-section in 3 of them, *abruption placenta* in 2, fetal distress 2 two and worsening maternal condition in 2 subjects. All neonates had Apgar score at five minutes above 7. The mean weight of birth was 2,099 g. Further results for perinatal outcomes in women who became pregnant undergoing hemodialysis are shown in Table 2.

Table 2. Perinatal outcomes in women who became pregnant on hemodialysis

Perinatal outcomes	n	%
Complications during pregnancy*		
Preterm labor	6	42.9
Polyhydramnios	5	35.7
Fetal growth restriction	3	21.4
Hypertension	13	92.9
Gestational age at delivery		
Less than 30 weeks	2	14.3
30 to 33 + 6 weeks	2	14.3
34 to 36 + 6 weeks	6	42.9
37 or more weeks	4	28.6
Birth weight		
<2,500 g	11	78.6
>2,500 g	3	21.4
Mode of delivery		
Vaginal	4	28.6
C-section	10	71.4

*some women had more than one complication.

Discussion

Maternal and neonatal outcomes in women who became pregnant undergoing hemodialysis treatment presented in this series of cases are worse than in the general population. However, a few decades ago the occurrence of pregnancy in these women was not even possible. Changes in renal replacement therapy allowed relevant improvement in their health and therefore in their quality of life. Therefore, pregnancies, even if mostly unplanned, began to occur.

In our study, the main causes of CKD in these women were chronic hypertension and glomerular disease. With the improvement of renal replacement therapy in the last 20 years, the percentage of women of childbearing age increased from 10 to 42%⁶. Thus, the pregnancy prevalence of women on dialysis is expected to increase, showing the importance of the topic. It is known that the rate of live births in this group of women have increased 40 to 50%, but the neonatal mortality rate remains high (8–13%)^{4,5}.

In our series, 7/14 women had hypertension as the cause of kidney function loss. During pregnancy, 11 women needed antihypertensive treatment throughout it and one of them used only late in pregnancy by the occurrence of preeclampsia. An Italian series that followed 23 women found similar results with half of the patients being hypertensive at the beginning of pregnancy (12/22 with available data), and 14/22 were hypertensive in pregnancy and throughout this study there was even a maternal death from cerebral hemorrhage (1 year after delivery)¹¹.

Pregnancy, itself, may aggravate CKD. The most important determinant of renal function are the creatinine levels, which decrease during pregnancy when compared to preconception levels⁵ and many studies have targeted the best values as limits to indicate renal replacement therapy. Women with creatinine levels between 1.2 and 1.4 mg/dL have a greater risk for gestational adverse outcomes than those with normal renal function. When pre-conception creatinine level is in the range of 1.4 to 2.5 mg/dL, there is a risk of 20 to 30% of preeclampsia and preterm delivery. However, if they are higher than 2.5 mg/dL, women should be discouraged from getting pregnant, since they would have a 70% risk of preterm delivery, 40% of preeclampsia, and 40% of decrease in renal function, either during pregnancy or in the post-partum period, foremost indicating dialysis^{2,5}. Ideally, therefore, the preconception creatinine level target is less than 1.2 mg/dL.

It is known that, when necessary, dialysis should be rapidly instituted since urea, creatinine and other metabolites cross the placenta. Thus, the number of dialysis sessions should be increased (from 5 to 7 per week) and extended for a minimum of 20 hours per week, targeting plasmatic urea level of 30–50 mg/dL^{5,7,8}. Moreover, with more frequent sessions, less volume is withdrawn in each session, reducing the risk of maternal hypotension and its fetal impact^{3,8}.

The implementation of more frequent dialysis sessions (5 to 6 per week), use of erythropoietin and control of hypertension, maternal and neonatal outcomes were satisfactory, although the complications were higher than in the general population, as showed in this study.

The most common complications herein were worsening maternal hypertension, polyhydramnios and pre-term labor, as well as shown in recent literature¹². One woman (the worst outcome in this series) developed malignant hypertension, with fetal growth restriction, preterm delivery at 29 weeks for fetal distress. Others due to maternal hypertension in this study were 2 *abruption placentas* and 2 women with acute pulmonary edema¹³.

The occurrence of polyhydramnios in this group is probably related to maternal uremia. An important cause of preterm labor in CKD under hemodialysis during pregnancy is polyhydramnios and this occurs mainly for two reasons: hypovolemia during dialysis causes decreased oncotic pressure and increased maternal urea leading to osmotic diuresis of the fetus^{2,14}. The incidence of polyhydramnios is estimated around 30–70% of these cases⁷.

Prematurity, either resulting from preterm labor or anticipated resolution due to maternal indications, is the major cause of neonatal morbidity and mortality^{10,15}. In our study, 49.2% of women had pre-term labor, and 71.5% (10/14) delivered under 37 complete weeks of gestation, however only 4 of 14 had it in 34 weeks of gestation.

Our neonatal outcomes were better than the ones of a Chilean series of 6 cases that had all preterm births with an average gestational age of 33 weeks (± 1.7). In this study, the most common cause of pregnancy termination was intrahepatic cholestasis of pregnancy, in 4 of the 6 cases. This is a serious complication of pregnancy, however it did not occur in any of the cases followed in our institution. One case of oligohydramnios, other of polyhydramnios and 1 intrauterine growth restriction were also recorded¹⁶.

In addition, regarding prematurity, which is the most relevant neonatal complication among women with CKD undergoing hemodialysis, the Italian series found 19/21 preterm, being 7/21 below 34 weeks, average weight and gestational age of the newborns were also worse than those found in our study¹¹.

A recent large case series with 22 Canadian and 70 American women provided better results. For the group of the Canadians cohort, the live birth rate (86.4%) was significantly higher than the rate in the American cohort (61.4%). Gestational age at delivery was 36 weeks (32–37) for the Canadian cohort compared with 27 ones (21–35) in the American. This study concludes that pregnancy may be safe and feasible in women receiving intensive hemodialysis¹⁷.

No one knows for sure if the relation between the onset of preterm labor during hemodialysis is, indeed, a consequence of this treatment. However, it is known

that there is a decrease in serum progesterone during this procedure of about 10%, and this could be one of multiple justifications for early labor⁸.

Concerning the mode of delivery, in this study, as well as previously reported in the literature, C-sections are more common^{4,6}. In that series, it occurred in 64.3% of women, better than the 100% reported in the Chilean cohort¹⁶. Cesarean indications were previous C-section in 3 of them, *abruption placenta* in 2, fetal distress in 2 and clinical maternal condition in 2. In one Chilean series, all six cases being followed-up were delivered by C-section.

Regarding neonatal outcome, all neonates had Apgar score at five minutes above 7, the average birth weight was 2,099 g and 71.5% were preterm (gestational age at delivery under 37 weeks). Due to the complications of hypertension, LBW was normally found in this group of women^{4,9}. As said before, the rate of perinatal complications still remains high.

To improve prognosis, the following are needed: a multidisciplinary team, strict control of serum urea and hemoglobin levels, and also maternal blood pressure as well as close monitoring of fetal growth and vitality⁴.

Another important strategy is the preconception guidance. All women undergoing dialysis should

be counseled about the possibility of pregnancy and its risks, and should use contraception to avoid unwanted pregnancies¹. If they become pregnant, immediate referral is needed towards a high-risk prenatal multidisciplinary team prepared for possible complications.

A limitation of this study is the restricted number of cases. Although it is an increasing condition, due to better assistance, more women undertaking dialysis are becoming pregnant; however, it is still rare.

The evolution of renal replacement therapy had an important impact in the fertility rate of women under CKD, and, therefore, pregnancy rate. Studies show that more frequency and more prolonged hemodialysis, as well as follow-up with multidisciplinary teams improve gestational results. However, perinatal complications remain high, specially worsening of maternal hypertension, polyhydramnios, and preterm births and its consequences.

Therefore, more studies need to be performed in order to compare different populations around the world and several dialysis control methods, probably as a multicenter study, enabling us to learn more about the outcomes and therapeutics. Obstetricians should be prepared for the increase in this condition.

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